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THE SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS, A TWENTY-YEAR-OLD SECTIONAL OBSTETRICAL AND GYNECOLOGICAL SOCIETY*

Presidential Address

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BY A very remarkable coincidence, this society was born, almost to the hour, twenty years ago today. Realizing this fact, I thought it would be appropriate and interesting to review the history of the Association and discuss, briefly, its objectives. Although we are a young society compared with other local, sectional, and national organizations, after many growing pains we have attained a position of respect, dignity, and usefulness.

Let me preface my remarks with a personal note, for it is with mingled feelings of pride and humility that I appear before you today. I am proud to have been one of the Founder Fellows of this young but vigorous organization. I am also proud of the honor paid me by the members of the Association in making me the seventeenth president. I am humble because of a feeling of inadequacy when I think of my distinguished predecessors who have held this honorable office. I am also humble because of the realization that I have received much more from this society than I have given to it.

I should like now to pay tribute to the past presidents, secretary-treasurers, members, and friends of this society who have done so much toward its organization and growth and who have contributed so richly to our specialties of

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obstetrics and gynecology. I should like also to acknowledge our good fortune in obtaining and retaining the interest of many men of national and international reputation who have been guest speakers and are now honorary Fellows. They have done much to stimulate interest in our meetings and to inspire us in our study and practice of obstetrics and gynecology.

As you know, the American Board of Obstetrics and Gynecology was organized in 1930. This was the third American Board of Medical Specialists to be established. There are now approximately twenty boards of the various specialties. Among the purposes of this board are the improvement of the standards and practice of obstetrics and gynecology and the issuing of certificates, after thorough investigation and examination, to successful applicants. Soon after the formation of this board, interest in these specialties was greatly increased and the organization of regional societies took place. Ours is one of them.

Organization

Almost a quarter of a century ago, the idea for forming a regional society was conceived by several physicians in the South Atlantic states. These men, realizing the similarity of the problems and interests in this geographical section, foresaw the possibility of improving the practice of obstetrics and gynecology by an organization of physicians who were primarily interested in these specialties. The first document that I could find relating to this matter was a letter written by Dr. Robert A. Ross, then of Duke Hospital, Durham, North Carolina, dated October 23, 1937. It was sent to approximately 75 physicians residing in the states of Florida, Georgia, South Carolina, North Carolina, and Virginia. Since this letter furnished the foundation on which the Association was built and expressed the keynote of its purpose, I think it noteworthy to quote a part of it. In reference to other regional societies, Dr. Ross wrote:

"The meetings have a very large attendance, the papers are practical, critical, and scholarly and the gospel of good obstetrics and conservative gynecology is expounded. . . . We are anxious to get the opinion of men such as yourself who would naturally participate in the organization and maintenance of such an association, by attendance and scientific contributions. In no sense should 'just another' organization be sponsored. Do you agree with the advisability of the undertaking?"

Dr. Ross sent several other letters to these physicians. Finally, in a letter dated January 12, 1938, outlining the program for the organization meeting to be held at the Hotel Charlotte, Charlotte, North Carolina, on February 4 and 5, 1938, he stated: "This shall be a happy, helpful and economical organization."

This meeting was well attended and inspiring. There were 73 Founder Members: 8 from Florida, 14 from Georgia, 8 from South Carolina, 22 from North Carolina, and 21 from Virginia. Dr. M. P. Rucker of Richmond was temporary chairman and presided at the scientific meeting.

Dr. H. Hudnall Ware, Jr., in his presidential address to the Association in 1954 at the sixteenth annual meeting, very ably recounted the history of the first 15 years of the society. In this address, Dr. Ware properly gave credit to the following for their untiring efforts at the organization meeting: Dr. Robert A. Ross for arranging the program, Dr. Robert E. Seibels as chairman of the committee on constitution and by-laws, Dr. W. Z. Bradford as chairman of the committee on local arrangements, and Dr. Oren Moore, who presided at the organization meeting and banquet.

Actually, this is the seventeenth meeting of the Association since its organization in 1938. No meetings were held in 1943, 1944, and 1945 because of World War II. Dr. Oren Moore was president and Dr. T. J. Williams was secretary-treasurer during this time, and these men were responsible for keeping the organization intact throughout this critical period.

Growth

The growth of this society in stature and prestige has been gratifying. We began with 73 active members. Our active membership is now limited to 200. Today we have 196 active and 29 Emeritus Fellows, a total of 225. A few became disinterested and were dropped from the roll because of nonattendance. We are extremely proud of our 33 Honorary Fellows, who may be classed among "Who's Who" in North American obstetrics and gynecology.

There have been many changes in the constitution and by-laws which were revised in 1948. A committee with Dr. J. D. Guess as chairman did commendable work on this revision. Some of the changes made during the past 20 years are of interest. In order to compare the situation then and now, let me cite a part of the original constitution on the requirements for active membership. The applicant had to be:

One who showed that he had had adequate training in obstetrics and/or gynecology as a specialty, by postgraduate work as a resident of not less than one year in an acceptable institution and who had demonstrated his ability in his work and in his writings, or:

One who was a member of the teaching staff of a recognized medical school, or:

One who had been in active practice for more than 10 years, had achieved eminence as a specialist, and could substitute his clinical, teaching, and research work for the postgraduate work required, and:

One who declared that his practice was limited to obstetrics and/or gynecology if he resided in a city of more than 75,000 population. If he resided in a city of less than 75,000 population, at least 75 per cent of his practice must be restricted to one or both of these specialties.

Now an applicant must, among other requirements, be a diplomate of the American Board of Obstetrics and Gynecology with all of its implications, and he must participate in a scientific program on invitation of the program committee.

In 1948, there was established an annual award to be known as "The Foundation Prize" for the best thesis on some phase of obstetrics and gynecology. This award has been given on two occasions only, in 1949 and in 1950. No apparent interest has been shown in it since that time.

To anticipate the action of the Association at its business meeting today, I hope that another progressive change will be made in the constitution which will permit the admission of more younger applicants and at the same time keep the older Fellows active in the organization. In this way, we would have the benefit of a combination of the wisdom and art acquired by the older Fellows and the energy and scientific training of the younger Fellows which would continue from generation to generation as a perpetual evolution.

Prestige and Accomplishments

This organization has prestige, tradition, and accomplishments of which we can all be proud. It is of noble birth. It was conceived in the minds of "gentlemen of the old school." It had life breathed into it at the organization

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meeting by such distinguished specialtists as Drs. Walter Dannreuther, J. P. Pratt, and Rudolph Holmes, who later became our first Honorary Fellows. It has been nourished by many of our Honorary Fellows with their continued interest, loyalty, attendance, and contributions to our programs.

One of our past presidents, Dr. Bayard Carter, is now president of the American Board of Obstetrics and Gynecology. Many Fellows of this Association are members of, and some have held high offices in, national organizations of our specialties. All are outstanding in their communities and have been active in their state societies. In these positions, our members have been able to maintain our prestige and to contribute to better knowledge and practice of our specialties.

Many of our members are heads of departments or are in teaching positions in medical schools and hospitals. Here they have opportunities to improve the caliber of our specialists in obstetrics and gynecology and to stimulate their interest in the South Atlantic Association. As a matter of fact, we are all teachers by precept and example.

The individual Fellows have done much in their home communities to impress other physicians with the excellent quality of obstetrics and gynecology that can and should be practiced. They have cooperated with their local Boards of Health and have aided tremendously in the marked reduction in maternal and perinatal mortality rates in the last 20 years.

Based on information received from authoritative sources of the five states composing this Association, I arrived at some interesting conclusions. The following figures are approximate and represent an average of the five states, based on statistics for the years 1937 and 1956. They show a comparison of the statistics for the year before this Association was organized with those after it had been active for 19 years. The population has increased 40 per cent. The birth rate has increased 4.6 per 1,000 population. There were approximately 200,000 more live births in 1956 than in 1937. The number of hospital deliveries has increased 58 per cent. Home deliveries by physicians have decreased 38 per cent and deliveries by midwives have decreased 20 per cent. The maternal mortality rate per 1,000 live births has dropped from 6.6 to 0.8, a decrease of 5.8. The perinatal mortality rate dropped from 70 to 34 per 1,000 live births, a decrease of 36.

I hope this brief account of the organization, growth, and accomplishments of the Association has been as interesting to the Founder Fellows, to those who have since become Fellows, and to our guests, as reviewing the records has been to me. We should, however, remember the cliché, "The past is prologue," and focus our attention on the future. We are privileged to be members of this organization and we should realize that along with privileges come obligations. Therefore, we as individuals are obligated to further the objectives of this society, a goal which we must reach if we are to match or improve on the national statistics. Are we going to meet this challenge of our professional responsibilities?

Objectives

Let us reflect for a few minutes upon the objectives of a sectional obstetrical and gynecological society—this one in particular.

The object of this Association is printed on the flyleaf of the annual program in order to keep us reminded of our purpose. This, briefly and essentially, is to study the problems and to improve the practice of obstetrics and gynecology by our members and by all other physicians residing in our territory. As I have just indicated, a great deal has been accomplished in this area during

the past 20 years toward the establishment of obstetrics and gynecology as specialties and the reduction of maternal and perinatal mortality rates. The members of this society have contributed much to this state of affairs. Then what more can we do as an organization and as individuals to further our objectives?

There is much that can be done through our efforts and influence in the fields of education and practice that would help solve some of the problems and improve our service to patients. The latter, after all, is our primary mission. We as teachers and practitioners, however, cannot live in ivory towers. The problems of those in teaching positions and those in private practice are somewhat different but our ultimate goals are the same. Realistic understanding and sympathetic cooperation between the two groups would help tremendously in accomplishing our purpose.

In order to stimulate thought and possible action, I should like to suggest that we consider our objectives in simple terms of supply and demand. If there is an adequate supply of able and conscientious obstetricians and gynecologists and a demand by the public for their services, much will be done toward accomplishing our purpose.

Supply.—By careful selection and teaching of medical students and training of interns and residents, we should have the highest type of specialists to carry on the teaching and practice of obstetrics and gynecology in our territory.

That medical education is in a state of flux is evidenced by the numerous articles in the journals and by the experimentation going on in various schools and hospitals. Dissatisfaction with education has been expressed by educators, practitioners, and the general public. The value of a cultural background, including greater emphasis on the study of the humanities by premedical students, is being recognized.

Our members who hold teaching positions are the ones we must rely upon to inspire, teach, and train students to be, first of all, doctors of medicine and then specialists in our chosen fields. These teachers must realize that they will always be remembered by their students as examples of character, personality, and ability.

In order to become a well-rounded specialist in our fields, the student should receive adequate instruction and training in general medical diagnosis, psychiatry, endocrinology, urology, abdominal surgery, and office gynecology. Research, writing, and public speaking should be encouraged.

Most of us in this organization are in private practice. Our education and usefulness can be furthered by the accumulation of knowledge and wisdom acquired by continued study and experience. It has been said, "Each one of us, however old, is still an undergraduate in the school of experience. When a man thinks he has graduated, he becomes a public nuisance." Ours should be a lifetime of growth and development. As our finite minds receive more insight into problems of research and practice, we shall be better able to render efficient service to our patients.

It is in practice that a physician ceases to be purely a biological scientist and technician and becomes a humanist also. He develops the art of the practice of medicine, a most gratifying accomplishment to both physician and patient. Someone has aptly said: "The man who knows 'how' will always have a job, but the man who knows 'why' will direct the job." The physician who knows "why" realizes that his patients are human beings, many of whom are plagued with emotional disturbances, and that they should be treated as a whole, both physically and mentally. He learns that laboratory tests should be "used to contribute to clinical judgment, not to replace it." With experience he develops "clinical sagacity."

Actually, in practice, our Fellows are providing excellent obstetrics and operative gynecology. The over-all picture, however, could be improved by using our influence in having and enforcing hospital rules regarding proper consultations and in having active records and tissue committees. We could also discourage the unnecessary and potentially dangerous use of sex hormones and antibiotics and the equally dangerous practice of unnecessary pelvic surgery.

The most neglected phase of our practice, in my opinion, is office gynecology. This is caused in part by the necessarily inadequate training in this phase of gynecology during residencies and in part by the fact that office gynecology is time consuming. In order to render adequate service to the patient, the gynecologist must practice so-called "comprehensive gynecology." It is in the office that he has his best opportunity to render a great service to the women of our area, especially to those whose gynecological complaints are caused, or aggravated by, emotional conflicts and anxieties. Currently, in the practice of medicine, there is a return to the psychosomatic concept.

In training our students and ourselves, we shall be better able to supply proper obstetrical and gynecological services.

What about the demand for our services? This is a matter of public education.

Demand.—Obstetrics has become well established as a specialty in the minds of the laity. Many deliveries, however, are still being done by general practioners, most of whom are aware of their limitations. In cases of difficulty, too often a general surgeon is called in consultation instead of a well-qualified obstetrician. Naturally, this practice results in many unnecessary cesarean sections and obstetrical cripples.

Obstetricians have a great opportunity to further the cause of preventive gynecology to the benefit of the women of their communities by insisting that their postpartum patients have semiannual checkups.

Gynecology, unfortunately, is not so well established as a specialty in private practice in some of our localities. It is amazing how few people know what gynecology is. Because of this situation, women are not aware that they should and probably would receive better treatment of their pelvic complaints from gynecologists than they would from physicians in some other fields of practice.

We are experiencing a changing philosophy of medical education and practice. What is to be the future role of the gynecologist? Will he accept referred patients only and be concerned chiefly with pelvic surgery or will he become known as a "women's doctor," doing "comprehensive gynecology" and acting as long-term medical adviser to female patients?

I hope that one of the national obstetrical and gynecological organizations will consider the advisability of preparing and distributing a dignified and informative brochure on obstetrics and gynecology to its members to be placed in their waiting rooms. This would be one efficient and ethical means of educating the public to demand the best obstetrical and gynecological service available.

The supply of well-trained obstetricians and gynecologists is increasing each year, but if the laity is not educated to demand their services, we are not improving the quality of obstetrics and gynecology in our territory to the fullest extent.

Conclusions

To further the accomplishment of our objectives and increase interest in this Association, it would be well for the active Fellows to realize that, as in

sports, religion, and other activities, one profits more as a participator than he does as a spectator. I would also suggest:

1. That the executive committee be ever alert to the study and improvement of hospital rules and of premedical, medical, and public education.

2. That, in arranging for the annual meetings, the program committee make a serious effort to plan programs which consist of practical papers and case reports and to provide opportunities for the Fellows to bring their problems for free discussion.

3. That the state committees be more active in affairs that would benefit the Association and the Fellows in their respective states.

The final objective of this Association is to "foster a spirit of comradeship and mutual helpfulness among those included in its fellowship." This purpose has been accomplished most effectively. I shall always be grateful for the opportunity of acquiring many of my most valued friendships through this Association. I wish for the Association and its Fellows many more years of useful service and happiness.

PHYSIOLOGIC CONSIDERATIONS IN LABOR AND THE PUERPERIUM*

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IT IS the common experience of those who have practiced clinical obstetrics for a number of years that one cannot depart from the physiologic pattern of reproduction without courting trouble. One after another, many who have had at one time or another enthusiasm for induction of labor, pentobarbital, caudal anesthesia, spinal anesthesia, etc., have abandoned or are abandoning these practices and returning to basically sound procedure.

The inevitability of complication in unphysiologic practice is the constant finding in the large surveys of maternal mortality in Philadelphia and other cities. It is noteworthy that those who work in these survey groups generally become the most conservative of obstetric practitioners.

It is possible that the uniting of gynecology with obstetrics has fostered a freer use of surgery on the assumption that "accouchement naturelle" is an old-fashioned business and needs "modernizing" to keep in line with the general progress of medicine. There is also a tendency to make the vagaries of obstetric practice fit the schedule of the busy clinician.

Throughout my medical life I have had a strong feeling for the physiologic in reproduction and have stated on numerous occasions[1] on platform and in classroom that there is no more need to interfere with the course of normally progressing labor than there is to tamper with good digestion, normal respiration, and adequate circulation.

However, the activities of any crusader in this field are endless, for when one false suggestion is thoroughly controlled, a dozen spring up in our prolific medical literature to take its place. Some years ago there was an internist who had inscribed on his gravestone, "He fed fevers." I should be very happy if some one would inscribe my epitaph, "He believed in physiologic labor."

This paper represents an effort to define what are significant physiologic considerations at delivery and determine why they should be respected and conserved. Some work that the author and the department have done in the past and some that is now in progress will be mentioned. Actually, however, it is amazing how little of fact is known about the simplest phases of reproduction. The field for research here is widely open.

*Address of the Guest Speaker, presented at the Twentieth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hollywood, Florida, Feb. 1 to 5, 1958.

The following are some present-day problems.

1. Can labor be safely induced?
2. What are suitable and safe analgesia and anesthesia in labor?
3. What is an efficient and comfortable position for obstetric delivery?
4. Do "routine" forceps contribute to a lessened morbidity and mortality?
5. What are the correct physiologic relations of the baby, the placenta, and the cord after delivery? How should the cord be handled?
6. What is the correct relationship of the baby and the mother in the hospital following obstetric delivery?
7. How can the newborn infant (and the mother) be protected from bacterial contamination in present-day hospital practice?

Induction of Labor

In spite of the fact that no one knows the cause of labor, there are a fair number of obstetricians who feel they can start it regularly and safely. The more conservative of these set up conditions for induction (engaged head, effaced cervix, dilatation of 2+ cm.) that sound like labor itself and I am not surprised at the degree of success under such circumstances. Unfortunately such fortuitous circumstances do not generally exist when one has a really urgent reason to induce labor, and then the percentage of success is much smaller.

Actually there is nothing very unusual or difficult about rupturing the membranes and inducing labor in a patient in whom it is likely to start spontaneously in a few days. One might suggest that we still have the matter of infection to consider and that rupture of the membranes opens the channel to it. Also we are running out of antibiotics. For those who use pituitary extract one might suggest that there are some instances of narrow placental reserve where hypoxia of the fetus will result and that ruptures of the uterus still occur under the stimulus of posterior pituitary extract (though never in reported series).

Probably we would all accept the fact that induction is indicated in some instances of pregnancy toxemia, in a few cases of postmaturity, and in an occasional patient who lives a considerable distance from the hospital.

I have no personal or departmental figures to present on this matter for, beyond the cases mentioned, we do not accept elective induction. One of our department members, Edward Bishop, has used elective induction in his personal practice and has written on it extensively and rather cautiously. He cites the usual percentages of successes and the usual precautions. Recently he told me that he was doing inductions less and less.

Analgesia and Anesthesia in Labor

From time immemorial, human ingenuity has sought some method of relieving the pangs of labor and the distresses of delivery. Conscious man in his desire for a more comfortable existence insists that woman is a fragile person, labor is a severe test and a method of relieving pain can be found and purchased.

On the other hand, Nature prescribes that birth is the most important physiologic event in life and that the newborn must be delivered free of incumbrance and depression. Analgesia and anesthesia is the field of conflict on which these two concepts meet and the result is a philosophy of compromise.

I have lived just long enough to have heard and seen something of twilight sleep, rectal anesthesia, barbiturate amnesia, continuous caudal, spinal,

pudendal block, and natural childbirth. Each of these was introduced with fanfare and enthusiasm, each was proclaimed to be the answer to parturient suffering, each was claimed to be free of danger to mother and depression to fetus; yet most of them have fallen into disuse or their use has become modified and cautious. In general, the reason has each time been the failure of the method to live up to the claims of efficacy and safety.

One of the saddest pages in American obstetrics had to do with the deep use of barbiturates. Quoting statistics from the Philadelphia Study, I pointed out this fact in a paper in 1937.[2] This paper had only to do with the maternal side of the picture. The fearful effect that these agents had upon hypoxia of the newborn in that day can only be guessed in the light of studies that Taylor has done in recent years.

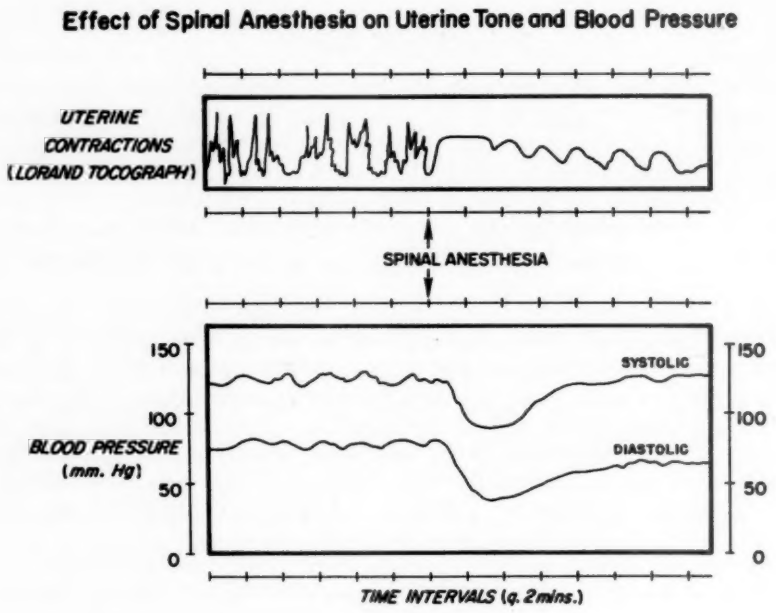

Fig. 1.

The most popular agents of relief today are spinal anesthesia, pudendal block, and gas-oxygen inhalation. Spinal anesthesia has possibly passed its peak of popularity. It has taken its toll of mothers' lives and it has certain innate undesirable effects which I summarized in a study of departmental cases in 1945.[15] Fig. 1 reveals one of its particularly undesirable effects in promoting hypertonicity of the uterus and hypotension of the vascular tree at the moment of administration. At the conclusion of that study I gave up the use of spinal anesthesia in vaginal delivery.

There is a great deal to be said, on the other hand, for the sound physiology of early marriage, early child-bearing, group instruction of pregnant women, adequate physician care during labor, modified natural childbirth, limited analgesia in labor, intermittent gas-oxygen anesthesia for delivery, and episiotomy under pudendal block.

Position for Delivery

Primitive woman squats or crouches at delivery.[4, 5] Medieval woman sat on an obstetric chair. During the Rennaissance she climbed into a high feather bed. The English parturient turned on her side. Present-day obstetric practice places women in the lithotomy position where forceps delivery and

episiotomy can conveniently be performed. Each of these attitudes and locations have certain advantages and disadvantages. Of our own recent spontaneous deliveries, 87 were done in the lateral position. We found that it offered certain advantages:

1. Comfort for the patient and lack of restraint while awaiting spontaneous delivery.
2. Release of pressure of the pregnant uterus on the vena cava.
3. Natural drainage of pharynx upon vomiting.
4. Facility of control of the advancing fetal head over the perineum.
5. Readier delivery of the shoulder girdle.
6. The best oxygen saturation pattern of the newborn of any type of delivery or position.[3]

Management of the third stage was found to be a trifle more difficult. When the placenta was delivered, the patient was returned to the lithotomy position for the repair of the episiotomy.

I think it may be quite possible to devise a delivery table or support that would be adjustable to almost any position or requirement in delivery including the extremely efficient squatting position. A mechanism of this kind was presented at one of the meetings of the American College of Obstetrics and Gynecology.

TABLE I. REPORT ON MATERNITY SERVICE

	JEFFERSON WARD* 1955-1957	JEFFERSON PRIVATE 1955-1957	MONTGOMERY AND BOWERS† 1954-1957	PRESTON RETREAT‡ 1954-1956
Adult discharges	3,001	2,886		
Births	2,395	2,622	737	1,091
Spontaneous vertex	2,046 (85%)	1,698 (64%)	584 (79%)	925 (85%)
Forceps, low	(5 mid-forceps) 157 (6%)	(4 mid-forceps) 618 (23.5%)	(3 mid-forceps) 95 (11.5%)	100 (9.1%)
Breech	86 (3.5%)	85 (3.2%)	23 (3.1%)	21 (2%)
Version	0	3 (0.1%)	0	1 (0.1%)
Cesarean section	105 (4.4%)	242 (9%) (Repeat 3.9%)	35 (4.7%)	30 (2.7%)
Maternal deaths	0	0	0	0
Perinatal mortality (Over 1,000 grams)	64 (2.7%)	49 (1.8%)	16 (2.1%)	19 (1.8%)
Full-term	24	20		
1,000-2,500 grams	40	29		
Fetal deaths	24	19	13	13
Neonatal deaths	40	30	3	6

*Ninety-five per cent nonwhite.

†Eighty-seven delivered in lateral position.

‡Ward service—largely white—843 spontaneous deliveries by nurse midwives. (Statistics provided by John C. Hirst, 2nd, M.D.)

Routine Forceps

I hesitate to reopen the controversy between "routine" prophylactic forceps and spontaneous delivery, and yet someone ought to ask now and then just what the universal application of forceps is supposed to accomplish for mankind.

Few will disagree that the transference of deliveries by high forceps, difficult mid-forceps, and internal podalic version to the cesarean section column has been for the good in lessening fetal damage. This leaves to the field of forceps some 10 per cent of cases in which true indication may arise from occiput posterior positions, tight pelvic outlets, and a few cases of inertia uteri. The remainder are so-called "prophylactic" or "routine perineal."

Some time ago we defined the level of "perineal" forceps as the station at which delivery will occur spontaneously 15 minutes later with gas-oxygen anesthesia and a liberal episiotomy. Whether these late perineal forceps save any fetal lives from terminal anoxia is highly questionable. Most of the fetal deaths in labor occur at a time when the situation is not amenable to relief or correction by immediate forceps delivery.

Table I sets forth a comparison of several delivery services in Philadelphia. The rate of forceps is low; the rate of cesarean section is higher than average, especially on the mixed private service. The perinatal mortality rate for births over 1,000 grams of 2 per cent is perhaps average.

Whether an increase of cesarean rate over 5 per cent provides a diminishing return still remains to be evaluated. However, one notes that the rate compounds when: (1) cesarean sections are done for fetal indications, to avoid hypoxia or fetal injury; (2) repeat section is practiced; (3) the number of repeat sections is not arbitrarily limited.

Relationship of the Baby, Placenta, and Cord After Delivery

Reynolds[6, 7] and others have pointed out the importance of delayed division of the umbilical cord as an enhancement to the mechanism of respiration at birth and the providing of the newborn with its full complement of blood.

In the undisturbed birth of mammalian species this mechanism is safeguarded by a natural train of events: (1) The birth of the offspring, (2) the birth of the placenta, and (3) the chewing off of the cord.

When the human animal began to develop his mechanical propensities and especially when man discovered the ligature, the pulsating umbilical cord became an inviting site to which to apply his new discoveries. As a result, prompt ligation and division of the cord after delivery became pretty much the rule.[6-8]

This artificial and unnatural procedure not only impaired the physiology of circulation and respiration at birth and deprived the baby of important stores of iron and hemoglobin, but it locked stagnant blood in the umbilical cord and made it an inviting site for infection.[9-11]

Infection of the baby by the umbilical cord route has recurrently been a serious problem in obstetric practice. Now with the recrudescence of hospital type infection and the failing control by antibiotics, it is becoming an increasingly important one.

Tables II, III, IV, and V reveal the preliminary results of studies on this problem that are now under way in our department, in comparing 5-minute ligation with severance and nonligation one hour after delivery.

TABLE II. CLINICAL OBSERVATIONS IN NONLIGATED CORDS
(Study in Progress)

Cord is limp, and bloodless, and usually there is no pulsation when cord is cut one hour after delivery
Cord desiccates sooner
Cord drops earlier
Histologic section at 24 hours reveals umbilical vein empty, umbilical arteries contracted and devoid of blood
Culture media for bacteria are reduced
Delayed slight bleeding must be watched for, and, if necessary, cord must be clamped or ligated
The longer the segment is left attached to the baby, apparently the better "living ligature" effect
Ultimate method of handling is not yet resolved

TABLE III. ORGANISMS CULTURED DURING "CORD STUDY"
(Study in Progress)

Escherichia coli—predominant	*Diplococcus pneumoniae*—1 time
Aerobacter aerogenes	*Streptococcus pyogenes* (β hemolytic) Lancefield Group A
Paracolon sp.	Streptococci (α, γ hemolytic)—predominant
Klebsiella—1 time	*Hemophilus influenzae*—2 times
Mima polymorpha—2 times	*Neisseria pharyngis*
Herellea vaginicola—6 times	*N. sicca*
Pseudomonas sp.	*N. catarrhalis*
Proteus vulgaris	Bacteroides sp.—4 times
Proteus mirabilis—1 time	Clostridium sp. (saccharolytic)—6 times
Proteus rettgeri—1 time	Clostridium sp. (proteolytic)—11 times
Alcaligenes faecalis—1 time	Gram-positive pleomorphic organisms unidentified—5 times
Enterococci—(α, β, γ hemolytic) Lancefield Group D	Veillonella sp.—1 time
Staphylococcus aureus—predominant	Gram-positive micrococci *(M. anaerobius)* 3 times
Staphylococcus epidermidis	

TABLE IV. HEMATOLOGIC FINDINGS AT 72 HOURS IN BABIES WITH LIGATED AND NONLIGATED CORDS
(Study in Progress)

	LIGATED (5 MIN. AFTER DELIVERY)	NONLIGATED
Hemoglobin	20.09 Gm.	22.1 Gm.
Hematocrit	62.3 per cent	66 per cent

TABLE V. BACTERIAL POPULATIONS OF LIGATED AND NONLIGATED CORDS
(SWAB FROM BASE OF CORD AT 72 HOURS)
(Study in Progress)

	LIGATED (57 CASES)	NONLIGATED (79 CASES)
Intestinal type organisms	80%	63%
Respiratory type organisms	28%	15%
Coagulase-positive staphylococci	68%	51%
Strict anaerobes	18%	10%

Clinical results and laboratory studies seem to favor the late severance and nonligation, though some instances of late cord bleeding have to be carefully watched. We have not fixed upon a final policy of cord management but are fairly sure that it will at least be in the direction of late severance.

Relationship of Mother and Baby Following Delivery

Under natural conditions in mammalian delivery, the newborn immediately seeks the mother's breast and nurses. Thereby the offspring learns to suckle and enjoys a sensation of security and protection. In the mother the process of nursing provides physiologic stimulus to the contraction of the uterus and the process of involution, and induces in the parent a sense of responsibility for the newborn. Thus there are established fundamental and important relationships of mother and infant.

As regards human reproduction, the relationship of mother and newborn has undergone considerable modification. In hospital delivery it is customary, for instance, to divide the umbilical cord a few minutes after delivery, carry the baby to another part of the delivery room or directly to the nursery, and return it to the mother's arms 12 to 24 hours later, depending upon the depth of anesthesia of the mother and the judgment of the obstetrician or pediatrician.

During this time and during his subsequent stay in the hospital the baby is placed in the nursery with some twenty or so other babies in various stages of newborn life, where it is presumed to enjoy the advantages of modern nursery practice and asepsis.

Just what advantages can ensue from this empirical method of dictating mother and baby relationship in the hospital is difficult to understand, for the nursery is neither sterile nor aseptic, and the personnel in the nursery is rarely adequate to cover the individual requirements of the many little patients who occupy it. Few babies accord to a rigid third- or fourth-hour feeding schedule and by the time the baby reaches the mother's breast twelve to twenty-four hours after delivery it may have lost much of its inclination to suckle.

Our own experience indicates that the baby does best that is kept at the mother's bedside. Since 1946 we have roomed all ward babies with their mothers from a few hours after delivery until the day of discharge. We have tried to encourage the private patient to do the same, although in the latter case the percentage of acceptance has been low. We have had epidemics of infection in the premature nurseries and the full-term private nurseries but not among the roomed-in babies of the obstetrical wards.

This observation is interesting in view of the many recent studies which have been made of staphylococcic hospital infections in operating rooms and central nurseries. Almost universally those who have written about such epidemics maintain that the quickest way to stop the epidemic is to separate all babies and place them with their mothers in a rooming-in pattern.[12]

Protection of Baby and Mother From Hospital Infection

How to protect the baby and its mother from hospital bacterial infection is one of the very important problems which faces the obstetric profession. With the increase of penicillin-resistant organisms, particularly of the coagulase-positive *Staphylococcus aureus,* and the diminishing number of antibiotics which are effective in the control of bacterial infections, significant organisms are found in the obstetric nurseries as well as on the surgical floors. These bacteria are evidentally brought to the nursery by personnel, are picked up by the nasopharynx of the newborn, and are disseminated through the area of the nursery to most of the babies during the five- or six-day nursery stay.[13, 14]

It has been fairly well demonstrated that these organisms from the nasopharynx of the baby enter the mammary ducts in nursing and constitute the most important etiological factor in mastitis and breast abscess in the mother. The same organisms may produce in the newborn infant serious pyoderma and pneumonitis.

TABLE VI. COMPARISON OF INCIDENCE OF COAGULASE-POSITIVE STAPHYLOCOCCI IN ROOMING-IN VERSUS CENTRAL NURSERY CARE
(Study in Progress)

Total number of infants studied	106
Ward full-term	51
Ward premature	2
Private full-term	51
Private premature	2

Plus mothers, physicians, visitors, hospital personnel, and all contacts

	Ward	*Private*
Complete rooming-in	51 (96.3%)	0
Partial rooming-in	0	11 (20.7%)
Central nursery care	2 (4%)	42 (79.2%)
Bottle-fed	10 (19%)	38 (71.6%)
Breast-fed	42 (79.2%)	15 (28.3%)
Combination	1 (2%)	0

We have under way in our own department a comparative study of the bacteriology of the newborn in the rooming-in segment of the ward and in the nursery areas of the private floor. Mothers, nurses, interns, residents, student clerks, hospital personnel, housekeeping personnel, and all other contacts are being studied. The phage typing of these staphylococci has not yet been completed, but the preliminary results with the coagulase-positive *Staphylococcus aureus* are set forth in Tables VI, VII, and VIII.

TABLE VII. COMPARISON OF INCIDENCE OF COAGULASE-POSITIVE STAPHYLOCOCCI IN ROOMING-IN VERSUS CENTRAL NURSERY CARE. PERCENTAGE OF POSITIVE CULTURES
(Study in Progress)

	WARD	PRIVATE
Cultures on Mother		
Nasal (on admission)	38	47
Vaginal (on admission)	26	16
Hands (1st feeding)	42	62
Breast milk (3rd day)	50	35
Nasal (on discharge)	54 (3rd day)	58 (6-8th day)
Cultures on Newborn		
Nasal (on discharge)	80	98
Paraumbilical skin (on discharge)	52	80
Cultures 8-12 weeks later		
Nasal (mothers)	66	62
Nasal (babies)	83	81

Cases of Morbidity.—

1. Labial furuncle—started 5 days prior to admission (Private)
2. "Cold sore"—lip of mother (Private); axillary abscesses in baby 5th day
3. Cervical lymphadenitis—baby 3 weeks after delivery—reported not serious (Private)
4. Breast abscess—3 weeks after delivery (Ward)

TABLE VIII. COMPARISON OF INCIDENCE OF COAGULASE-POSITIVE STAPHYLOCOCCI IN ROOMING-IN VERSUS NURSERY CARE. POSITIVE CULTURES IN PERSONNEL
(Study in Progress)

	TOTAL NUMBER	PER CENT POSITIVE
Staff	34	64
Residents and interns	13	78
Nurses	62	70
Student clerks	23	65
Housekeeping and aides	17	82

It would appear from these preliminary studies that the rooming-in arrangement of the obstetric wards has a slight advantage over the central nursery in the private floors. However, as significant bacteria become disseminated in all parts of the hospital, this difference is probably becoming of less and less importance.

Quite likely it will not be long until the general population are at one time or another carriers of pathogenic staphylococci and the home may not be a much safer place than the hospital. In the meantime, however, careful consideration must be given to ascertaining the best fashion of protecting the mother and the newborn infant. While the hospital provides an ideal environment for the handling of obstetric delivery and various intrapartum complications, it certainly does not provide an adequate area for the care of the newborn and the parturient. We probably would be in much better position if patients were admitted to the hospital for labor and delivery, their babies placed with them in individual rooms after delivery, and the mother and baby discharged for home care within twenty-four to thirty-six hours.

In the meantime, methods must be developed for protecting the newborn from the entrance of pathogenic staphylococci into the respiratory tract, skin, and umbilical cord. It may well be that we have as significant a problem facing us in the future in regard to fetal morbidity from infection as Semmelweiss had to deal with many years ago in puerperal infection of the mother.

Conclusions

Most of the space in this paper has been devoted to a consideration and criticism of unphysiologic practices in obstetrics. The question may well be asked, What does the author consider basic physiologic procedure in obstetric delivery? These principles may be set down as follows:

1. Early marriage and early childbirth should be encouraged. It is at this period of life that a woman is best able to have her children and labor is usually less complicated.

2. Pregnant women should be instructed as to the physiology of pregnancy and labor and the care of the newborn infant in class instruction.

3. Labor and delivery are probably best accomplished in a maternity hospital or the maternity wing of a hospital where the facilities for safe conduct are provided.

4. Analgesia and anesthesia for labor and delivery must be accepted as a compromise with physiology. As such, these agents should be kept to a minimum in order not to interfere with the physiology of respiration of the newborn or the vitality of the mother. Frequent presence of the physician constitutes the best support of the patient in labor.

5. Arrangements may be made for the presence of the husband in labor or delivery as the couple desire. This often constitutes additional support and comfort to the patient.

6. Spontaneous delivery should be expected to occur in about 85 per cent of cases. There seems no reason for operative interference where the course of labor is proceeding physiologically and mother and baby are tolerating labor well.

7. Episiotomy performed under local anesthesia or pudendal block facilitates the delivery and its careful repair returns the reproductive tract to satisfactory condition.

8. Upon delivery the baby should be kept at a level 6 to 8 inches below the uterus and subsequently in a level below the placenta. The cord need not be severed until one hour after delivery and then may or may not be ligated.

9. At the conclusion of delivery and the repair of the episiotomy the baby may be placed at the mother's side for her to nurse and fondle.

10. Baby and mother should be placed in a safe isolated area for immediate postoperative examination and then roomed together in the mother's quarters until discharge from the hospital.

11. Well babies and well mothers may be discharged from the hospital twenty-four to thirty-six hours after delivery for puerperal care in the home.

12. Further research is required in the future into the nature of the physiologic processes which underlie reproduction and their significance.

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A REVIEW OF THE AGGRESSIVE MANAGEMENT OF ABORTION*

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ABORTIONS, both spontaneous and induced, have probably always been of concern to women. Early writings and legends are replete with material on the abortion concepts and practices of primitive people.

Since the dawn of recorded history, induced abortions are repeatedly described. Himes[1] has called attention to what may be the oldest described abortifacient recipe dating back some 4,600 years to the Chinese Emperor, Shen Nung, 2737-2696 B.C. While the old Babylonian scripts evidenced no interest in the induction of abortion, the famous Egyptian writings, the Ebers Papyrus, gave full directions as to the manner of producing an abortion and indicated that this procedure was well known to the Egyptians. Turning to the Greek civilization, we find discussions of both induced and spontaneous abortions. Hippocrates saw much of the injury to life and health produced by these efforts. While willing to condone abortions and even to advise the interruption of pregnancy, he was opposed to putting these agents into the hands of the laity. Apparently Hippocrates considered therapeutic abortion as a rather unpleasant but necessary expedient.

When we compare the writings of the philosophers Plato and Aristotle with those of Hippocrates and other physicians, we find a contrast not unlike that found between sociologists and physicians of today.

The practice of abortion among the Greeks was evidently quite common and their attitude was apparently casual. According to Taussig,[2] the practice of abortion was one to which few persons in antiquity attached any significant feeling of condemnation.

In the early days of the Roman Empire abortion was rare, but in imperial times it grew without restraint, and apparently was accepted as a natural consequence of the unrestrained sexual life of the era. The only limitation seemed to be that the father of the child had the right to determine the abortion.

The tribes of Northern and Central Europe looked with disfavor on any limitation of their number through abortion, and the Visigoths punished the abortionist by death.

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The philosophy of the Christians was very different, however. With unwavering consistency and with the strongest emphasis they denounced the practice, not only as unchristian but as inhuman and murder. In the fourth century, Priscianus, a Roman physician, declared that no one had the right to prescribe any means for producing an abortion. He felt that a physician should not burden himself with this sin and that only when the uterus was diseased or the mother was exposed for other reasons to dangers through pregnancy was an abortion permissible.

In the succeeding centuries, the effect of the church became stronger and induced abortion was almost universally denounced. The control of conception and excessive numbers of pregnancies or the need for family limitation slowly shifted to contraception and sterilization in its many forms. The interruption of pregnancy came to be placed in an extralegal, if not extramoral position, and such interruptions have been termed "criminal" except when the health of the mother was involved.

Recently several nations have authorized the interruption of unwanted pregnancies through state or private means under certain circumstances. In this country the dominance of Christian thought has prevailed, and while the statutes of the several states permit interruption of pregnancy—therapeutic abortion—the factors are reasonably well limited to medical issues.

Thus we find that the twentieth century concepts are similar to those of early Greek civilization, the physician recognizing a medical need and the philosophers, social reformers, and the public demanding a more liberal approach to this procedure of pregnancy limitation.

When we turn our attention to the procedures for inducing abortion as opposed to the philosophy of abortion, we find a steady trend to the more direct approach.

Following incantations and mysticism came physical exercise, hot baths, drugs, and, eventually, instrumentation and intrauterine injections.

As the history of the medical approaches to abortion is reviewed, it is seen that the priests and midwives were often thought to have control over the pregnancy. Efforts were made to induce an evil spirit to destroy the embryo of an unwanted pregnancy. When these were found wanting, starvation, ingestion of bitter foods, or the use of drastic purgatives were alleged to be useful in producing abortions.

As the early peoples contemplated the need for population control and the elimination of unwanted pregnancies, they turned first to infanticide. This was accomplished by both neglect and direct attack. It was observed that some infants were born too early to survive, and that the onset of labor often followed the loss of amniotic fluid. It was but a short step indeed to intentional amniotomy at a previable stage of pregnancy.

This was the practice in early recorded history for the destruction of an unwanted pregnancy. However, the natural, social, moral, and personal pressures involved in interrupting a pregnancy after "quickening" or "feeling life" soon pushed the time selected from the relatively safe interval of the middle trimester to the earlier first trimester.

Manipulation followed the expected anatomical course—first vaginal, then cervical, and finally intrauterine. Often there was an admixture of symbolism or mysticism and the mechanical, as when the old concept that "if something slippery was eaten, the fetus would slip out of the womb," was combined with the employment of slippery elm bark, with modest success.

Although the fungus ergot had been recognized as early as 600 B.C., it was regarded as a poison since its only known effect was gangrene of the extremities. Ergot was first mentioned as an obstetrical herb in 1582 by Lonicer[3] when he wrote that it caused "pain of the womb."

During the next 200 years, midwives used the drug extensively, but it was not until the latter part of the eighteenth century that its value in obstetrics was recognized by the medical profession.

The first physician to employ ergot was Desgranges[3] in the late eighteenth century but he did not publish his observations until 1818. By this time ergot was well known to expedite slow labors and was frequently used to save time for the accoucheur. During this period the drug was used extensively by midwives, not only in labor but also to cause abortion.

Aside from their social or moral aspects, abortions and the complications thereof continue to be a medical problem. Bleeding and secondary infection posed a real threat to the health of the patient, and the control of these two complications has occupied the attention of physicians and midwives for the past 250 years.

Hemorrhage, the more dramatic complication of abortion, attracted early attention. During the sixteenth and seventeenth centuries, the midwives were employing ergot, while physicians employed venesection, with the midwives eminently more successful. By the nineteenth century, however, physicians were also employing this agent with equal effectiveness.

The neglected and/or induced abortion frequently became infected with the development of the second dreaded complication, sepsis. Here the moralist returned to the scene and indicated that such complications were punishment for an immoral or criminal act. Hence, we find the term "criminal" and "infected" being used synonymously and "spontaneous" and "noninfected" likewise.

This was the state of affairs at the birth of gynecology in about 1875. As the gynecologist became more conversant with the anatomy and pathology of women, a more aggressive approach, usually involving a curette, became popular. While the curette promptly controlled hemorrhage, it inadvertently increased sepsis. Thus, the introduction of the gynecologist into the treatment of abortion produced somewhat of a dilemma.

By 1900, two schools of practice had developed in the management of incomplete abortions. The medical approach utilized primarily oxytocics, bed rest, and supportive therapy which predisposed to a somewhat greater blood loss but also a diminished incidence of sepsis, and the surgical approach with aggressive curettement promptly controlled bleeding but resulted more

frequently in the serious complication of sepsis. It appeared that the control of hemorrhage and the avoidance of sepsis could not be accomplished simultaneously. Both schools of thought exhibited large series of cases and each claimed superiority for its method of management.

In 1899, Hirst[4] advocated the following treatment for the infected bleeding incomplete abortion: use a sterile vaginal tampon to effect cervical dilatation; in 12 to 24 hours remove it and the gestational products that appeared in the cervix. Ergot was given by mouth and as soon as the cervical os would permit it, the uterine cavity was emptied under sterile conditions by the use of a finger wrapped in gauze. Following this, the uterine cavity was gently curetted.

This was the state of affairs at the turn of the century. Gradually, about 1920, the noninterventionists even abandoned oxytocics except for serious hemorrhage because it was thought that their use predisposed to the spread of infection by squeezing infected material out of the endometrial cavity into the venous sinusoids and parametrial tissue.

A sound concept of the control of postabortal sepsis was laid by Hofbauer[5] who, in 1926, described the development of a protective biological barrier in the broad ligament consisting of monocytes and phagocytes. He observes that it required from 72 to 96 hours for this to be effective and added considerable credence to the belief that uteri with infected abortions should not be curetted for some 72 hours in order to allow the formation of this body defense mechanism.

During the second quarter of the twentieth century, the concept of medical management became dominant and was generally accepted. Even the introduction of the sulfonamides and antibiotics tended to enhance the precepts of the "deferred" school. Such eminent clinicians as Bubis,[6] DeLee,[7] Schumann,[8] Reis,[9] Greenhill,[10] Beck,[11] Dyer,[15] in this country, and Kellar[12] in Scotland, and many others, all advocated medical management except in extreme hemorrhage. The concept of primary medical management of infected incomplete abortions was clinically well established, leaving intrauterine manipulations until the infection had been completely controlled.

In contrast to these medical regimens a small number of physicians continued to advocate the early curettement of incomplete abortions and good results were reported by Falk and Abelow[14] and others.

In contemplation of this difference of clinical opinion, it appeared that there must be some explanation for the good results reported by each school which was not being visualized or considered. The studies of T. K. Brown indicating the progressive infection of the uterine cavity following parturition suggested that the uterus of an abortion might likewise be sterile (or only contaminated) for 12 to 36 hours after the accident, that it becomes infected during the 48 to 72 hour interval, and then becomes sterile again as the biologic mechanisms come into play toward 96 hours, to contain the infection within the pelvis.

On further analysis it appeared that those clinics or physicians advocating the early use of the curette were usually treating private patients who were

seen early, and in whom infection was not a factor. The advocates of medical conservative therapy were usually those dealing with ward or charity patients with late abortions in whom infection had already become a primary problem. Whereas curettage could be effected with reasonable safety in the first group, the latter group were being compromised by a breakdown of protective barriers and a spread of the infection. Thus the results of both groups might truly be satisfactory, not because of the different management, but because the clinical material under consideration was different. Perhaps this was the true but occult difference in the two apparently different systems of management.

Thus, by mid-twentieth century, there had evolved two generally accepted principles for the management of the incomplete abortion: (1) The uterus must be emptied and (2) the patient must be supported and rehabilitated. All the variables of management have concerned the method, timing, and integration of these two principles of therapy.

The uterus may be emptied through necrosis and liquefaction, by uterine contractions with or without oxytocics, and by mechanical means. The issue is in the choice and timing of these methods of uterine evacuations.

The support of the patient involves rest in bed with fluid and food, replacement of blood, and assistance in controlling infection by antibiotics, and permitting the development of the biological barrier of Hofbauer.

Prior to 1956, incomplete abortions at the University of Arkansas Medical Center had been managed primarily by conservative medical means unless hemorrhage forced a curettage. Curettage usually was reserved until all evidence of sepsis had been absent for a period of 72 hours. Because of the continued bleeding in some, the spread of infection in a few, and the long period of necessary hospitalization in many, it appeared desirable to explore other methods of management.

It was thought that perhaps continuous infusion of oxytocics (Pitocin) would control hemorrhage and might empty the uterus in many cases. It seemed possible that a chemical or antibiotic barrier could be substituted for the biological barrier to contain and limit the infection. And it appeared possible that the rapid development of an antimicrobial barrier might permit an early and safe mechanical evacuation of the uterus. If this could be done without increasing infection, it would be greatly to the advantage of the patient. An attempt has been made to answer this question.

Material and Method

Beginning on July 1, 1956, the management of all types of incomplete abortions admitted to the University of Arkansas Medical Center became aggressive. As soon as the diagnosis of abortion was established, an intravenous infusion of 1,000 c.c. of 5 per cent dextrose in water with 3 c.c. of Pitocin and 1 million units of aqueous penicillin was started and run at a speed of approximately 250 c.c. per hour; if the bleeding increased, the rate of infusion was increased; at times a second or third liter of Pitocin-penicillin infusion was added. Any tissue found in the cervical canal was removed with ovum forceps. All patients were given 600,000 units of procaine penicillin and 500 mg. of streptomycin intramuscularly twice daily for 2 days. Routine preparation of the patient included an enema, hemoglobin determination, and urinalysis; blood loss was replaced as indicated.

A curettage was contemplated between 12 and 24 hours after treatment was started for all abortions which were thought to be incomplete. Surgery was not delayed in any case because of fever; nor was it necessary because of hemorrhage to curette a single patient prior to the planned interval. Occasionally operating room scheduling difficulties were encountered which delayed some of the curettages longer than planned.

All of the cases of abortion admitted to the Center from July 1, 1956, through June 30, 1957, have been reviewed. All of the 152 patients had been treated according to the above-described aggressive plan. (Seven patients were given Achromycin intravenously because of a history of penicillin sensitivity.)

The results of this aggressive management of abortion have been compared with those of the conservative management utilized at an earlier period. A review of the records were made of all of the 148 cases of abortion admitted to the University of Arkansas Medical Center during the 2 years, 1950 and 1951. These patients treated conservatively received, by comparison, minimal amounts of penicillin (usually 300,000 units daily) and streptomycin (500 mg. daily) intramuscularly. A few patients also received sulfadiazine, and 10 patients had no antibiotic treatment at all. Oxytocics (usually intramuscular Pitocin) were employed only to control hemorrhage, and an occasional patient required curettage for this purpose. Blood transfusions were given as indicated, many patients requiring subsequent transfusions to replace the further blood loss during the interval of observation and medical management. While most of these patients were ultimately curetted, the curettages were of a deferred variety; almost all of these women were afebrile at the time of operation, and had been afebrile from 48 to 72 hours.

TABLE I. GENERAL DATA

	CONSERVATIVE SERIES 1950 AND 1951	AGGRESSIVE SERIES 1956-1957
Total No. obstetrics-gynecology admissions	5502	3594
Total No. gynecology admissions	1167	817
Total No. curettements	270	299
Total No. abortions studied	148	152
Average age of patients	28	26.2
Total No. of pregnancies	870	967
Average No. of pregnancies	5.9	6.4
Total No. of abortions	240	290
Average No. of abortions	1.6	1.9

Comparability of the Control and Study Groups

Since this is a comparative study, an attempt has been made to compare the material in the two series. Table I gives the general data. Note that the total number of obstetric-gynecologic admissions to University Hospital in the two years of 1950 and 1951 is larger than in the one year of 1956-1957 (5,502 vs. 3,594); the total number of gynecologic patients in 1950 and 1951 was 1,167 as compared to 817; the total number of curettements was 270 in 1950 and 1951 as compared to 299 in 1956-1957. The total number of abortions studied was 148 in 1950 and 1951, 152 in 1956-1957. The increased number of abortions treated in 1956-1957 parallels the general increase in Departmental admissions consequent to the opening of the new facility. (In 1950 and 1951, some complete abortions were treated in the Emergency Room on an outpatient basis.) The average age of the patients in these series is similar, being 28 years in 1950 and 1951 and 26.2 in 1956-1957. The total number of pregnancies in 1950 and 1951 was 870 as compared to 967 in 1956-1957. The average number of pregnancies per patient was 5.9 in 1950 and 1951 as compared

to 6.36 in 1956-1957. The total number of abortions was slightly higher in 1956-1957 and this may be reflected in the difference in the average number of abortions between the two series plus some repeaters.

Table II demonstrates the clinical status of these patients. Forty-two per cent of the patients in 1950 and 1951 required transfusions on admission as compared to 26 per cent in the 1956-1957 series. The average number of days of symptoms prior to admission in 1950 and 1951 was 14.5 as compared to 6.4 in 1956-1957, suggesting that patients sought care at an earlier date in the latter series. In 1950 and 1951, there were 52 per cent febrile patients as compared to 33 per cent in 1956-1957. The slightly increased incidence of febrile patients admitted in 1950 and 1951 reflects the bed limitation of the earlier era. The total number curetted in each series is approximately the same.

While there are certain discrepancies between these two groups of patients, it is believed that they are sufficiently comparable to make clinical comparisons valid.

TABLE II. CLINICAL COMPARABILITY

	CONSERVATIVE SERIES 1950 AND 1951	AGGRESSIVE SERIES 1956-1957
Total No. of cases	148	152
Per cent of patients with significant anemia	42	26
Average No. of days of symptoms prior to admission	14.5	6.4
No. of patients febrile on admission or within 6 hours	78 52.7%	50 33%
No. of patients afebrile on admission	70 47.3%	102 67%
No. not curetted	43	39
No. curetted	105 73%	113 67%

Results

In an attempt to evaluate the new regime, several factors were considered. The first of these is the efficacy of the method of emptying the uterus; the second consideration is the conservation of blood; third is the control of infection; and the fourth and final criterion used to evaluate the aggressive form of treatment is the average duration of hospital stay. It seems apparent that prolonged sepsis (as indicated by fever of more than 6 days' duration), excessive blood loss (even though replaced by transfusion), retarded rehabilitation of the patient, and prolonged hospitalization would suggest a significant disadvantage of any method of management of abortion.

It is of interest that in the matter of evacuation of the uterus, the two series are remarkably similar, 71 and 79 per cent, respectively, requiring curettage. In the conservative series of 1950 and 1951, 43, or 30 per cent, of the abortions were completed during the period of medical management while approximately the same number (39) were completed under oxytocic therapy in 1956-1957. Even in the cases in which the uterus was emptied medically, the aggressive use of oxytocics and penicillin appeared to have considerably shortened the hospital stay, from an average of 6.5 days in 1950 and 1951 to 3.5 in 1956-1957 (Table III).

An evaluation of the effect of the aggressive form of therapy on blood loss is somewhat more difficult. In the conservative series, 64, or 43 per cent, required transfusions on admission, while only 39, or 26 per cent, required transfusion on admission in the aggressive series of 1956-1957 (Table IV). Fifty-six patients in 1950 and 1951 required oxytocics to control hemorrhage, and 3 required curettage. Eighteen patients in the conservative series required an additional 36 units of blood after they were under therapy, averaging 2 units of blood

per patient. No patients in the aggressive series required subsequent transfusions, for once the aggressive form of treatment was instituted, bleeding was effectively controlled. The total number of units of blood used in 1950 and 1951 was 177 as compared to 71 in 1956-1957, and the average number of units of blood per patient was 2.4 in 1950 and 1951 and 1.8 in 1956-1957.

TABLE III. METHODS OF EMPTYING THE UTERUS

	CONSERVATIVE SERIES 1950 AND 1951	AGGRESSIVE SERIES 1956-1957
Total No. of cases	148	152
Medical Treatment.—		
Not curetted		
Evacuation spontaneous (or by oxytocics*)	43	
Oxytocics		39
Average No. of hospital days	6.5	3.5
Curettement.—		
Curetted	105 (71%)	113 (74%)
Average No. of hospital days	8.8	3.0

*In 1950 and 1951 oxytocics were used only for hemorrhage in 79, or 53%, of the total series, and in 24 of 43, or 55%, of the patients not curetted.

TABLE IV. BLOOD LOSS

	CONSERVATIVE SERIES 1950 AND 1951	AGGRESSIVE SERIES 1956-1957
Total No. of cases	148	152
Total No. of patients transfused on admission	64 (43%)	39 (26%)
Total No. of patients transfused during therapy	18 with 36 units	0
Total No. of patients transfused	72	39
Total No. of units of blood used	177	71
Average No. of units per patient transfused	2.4	1.8

Fever is the third factor to be evaluated in a comparison of the efficacy of the aggressive series with that of the conservative series (Table V). Fifty-two patients in the conservatively managed group were afebrile on admission and were ultimately curetted. The average hospital stay for these patients was 10.3 days. In 1956-1957 there were 39 febrile patients who were curetted and their average hospital stay was 4.4 days.

TABLE V. FEVER AND SEPSIS

	CONSERVATIVE SERIES 1950 AND 1951		AGGRESSIVE SERIES 1956-1957	
Total No. of cases	148		152	
No. with fever on admission	78		50	
No. curetted		52		39
Average No. of hospital days*	9.2	10.3	4.0	4.4
No. with sepsis (6 plus days' fever)	5		0	

*Afebrile on discharge.

The incidence of sepsis (as indicated by fever of 6 or more days) in the two groups is of interest. In 1950 and 1951, 5 patients were infected, while in 1956-1957 no patients had fever of this duration. Thus it appears that, under the conditions of this project, the curettage can be done safely even in febrile patients, and to their advantage.

And last, is the matter of the duration of hospital stay for the two types of patient management. The average number of hospital days for all patients was reduced from 8.1 to 3.9 days by the aggressive approach (Table VI). It will be noted that for all patients curetted, regardless of whether they were febrile or not, the hospital stay was reduced by at least 50 per cent by aggressive management.

It might be added, at this point, that there were no deaths in either series.

TABLE VI. DURATION OF HOSPITAL STAY

	CONSERVATIVE SERIES 1950 AND 1951	AGGRESSIVE SERIES 1956-1957
Total No. of patients	148	152
Febrile patients	78	50
Average No. of hospital days	9.1	4.5
Medical treatment	7.1	4.5
Curetted	10.3	4.4
Afebrile patients	70	102
Average No. of hospital days	7.1	3.5
Medical treatment	5.6	3.2
Curetted	7.4	3.7
Patients not curetted	43	39
Average No. of hospital days	6.5	3.5
Curetted patients	105	113
Average No. of hospital days	8.8	3.0
Average No. of hospital days for all patients	8.1	3.9

Comment

Some problems have been encountered in the attempt to compare these two series of patients. It appears that the patients were seeking treatment somewhat earlier in the aggressive series, perhaps because of the availability of hospital beds, thereby somewhat lessening the number of seriously ill patients admitted. Also, more effective antibiotics may have contributed to a better method of chemical sterilization of the infected uterus. Both groups, however, were composed of a similar type of patient (ward), and all patients in each group were managed in essentially the same manner. Thus it is believed that because of the hemogeneity and size of the two groups, they are essentially comparable.

From these figures, several factors seem to be established: (1) Bleeding can be controlled by the aggressive use of oxytocics and early curettement. (2) Infection appears to be controllable for there were no patients with sepsis in the aggressively managed group. (3) There is a definite enhancement of rehabilitation through this more aggressive form of therapy. These items are apparent not only in the decreased patient morbidity and blood loss but also in the decreased number of hospital days per patient with its attendant economy.

These preliminary but successful results from the aggressive form of therapy appear to substantiate our belief that oxytocics can control bleeding promptly and that they often will evacuate the uterus within a few hours. Also, deferring the curettage for 12 to 24 hours provides an opportunity not only for hydration of the patient and giving of calories, but for correction of any electrolyte imbalances and replacement of any significant blood loss. The intravenous administration of the relatively large doses of penicillin insures a prompt high blood level which is supplemented and sustained by the intramuscular administration of the antibiotics. During this interval the patient's condition becomes stabilized, and she can be properly prepared for anesthesia and operation. And, finally, the early curettement assures completion of the abortion.

Conclusions

These studies suggest that, in incomplete abortion, an antibiotic barrier can be substituted for the natural biological barrier to infection, thus permitting a safe and early mechanical emptying of the uterus. This is to the patient's advantage from the standpoint of health and economics.

Summary

1. A series of patients with incomplete abortion at the University of Arkansas Medical Center has been studied.

2. Two methods of management have been compared: 148 patients treated in 1950 and 1951 by the time-honored conservative or medical method, and 152 patients treated in 1956-1957 by an aggresisve combination of the prompt use of antibiotics and oxytocics, followed by mechanical emptying of the uterus (within 24 hours).

3. The aggressive clinical program resulted in diminished blood loss, decreased incidence of sepsis, and decreased length of hospitalization.

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THE POSSIBLE ROLE OF SMEGMA IN CARCINOMA OF THE CERVIX*†

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THIS is an interim report of a study begun in 1950 to determine any possible role human smegma might play in cancer of the cervix. The preliminary report[1] was published elsewhere in 1956.

Several epidemiological studies of cervical cancer have recently been made,[2, 3] investigating multiple social, hereditary, and environmental factors. Most evidence points to a correlation between cancer of cervix and marriage at an early age, unrepaired cervical lacerations, low economic status, and uncircumcised marital partner. Little definite statistical association between the number of pregnancies, douching with coal tar products, and diet has been obtained.

It has been reasonably well established that Jewish women have low rates of cervical cancer.[4, 5] Most authorities agree that this is not due to the Mosaic laws for menstruation, as it is estimated that very few (5 per cent) Jewish women observe the laws of Nidah. Religious circumcision of the male is thought to be an important factor. Cancer of the penis has never been reported in a patient properly circumcised in infancy. This disease is also very rare in anyone circumcised during childhood.

Handley[6] has called attention to the low incidence of cancer of the cervix among Fijis. The Indians of the Fiji Islands who do not practice religious circumcision have an incidence eight times as great as that of the Fijis who do practice circumcision.

The observation that cancer very rarely occurs in nuns may indicate at least one compensation for permanent virginity. Homburger[7] feels this immunity may not be the result of abstinence from sexual intercourse but might be an indication of the need for stimulation of the cervical epithelium by pregnancy before cancer can develop.

Our results with the use of the Papanicolaou smear screening technique in one thousand consecutive clinic patients and one thousand consecutive private patients (Table I) are in agreement with those of most workers in this field. This threefold incidence of carcinoma in the clinic group over the

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private group supports the low-economic-group theory. We have noted that not only is the incidence of carcinoma higher, but the smears show a higher percentage of other cellular aberrations than is found among the private patients. This group is predominantly Negro (98 per cent) with coitus at an early age, unrepaired cervical lacerations, and poor vaginal hygiene. It has been impossible to ascertain the number of uncircumcised sexual partners in this group, but it is undoubtedly high.

TABLE I. PAPANICOLAOU SMEAR SCREENING TECHNIQUE IN 1,000 CONSECUTIVE SERVICE CASES AND 1,000 CONSECUTIVE PRIVATE CASES

Service.—

952 Negative Smears (cervical)
1 case hyperplastic cells, negative biopsies
47 cases questionable diagnoses
8 cases doubtful cells
3 doubtful, later biopsy, carcinoma
3 doubtful, later biopsy chronic cervicitis
2 doubtful, no follow-up
14 cases suspicious cells
7 suspicious, carcinoma
4 suspicious, chronic cervicitis
3 suspicious, no follow-up
25 cases carcinoma cells
22 carcinoma cells, carcinoma
1 carcinoma cells, leukoplakia of cervix
1 carcinoma cells, chronic cervicitis
1 carcinoma cells, terminal cancer of breast
Incidence, 3.2% carcinoma

Private.—

984 negative cervical smears
4 cases hyperplastic cells, negative repeat smears
12 cases questionable diagnoses
5 cases suspicious cells
3 suspicious, negative follow-up
2 suspicious, cancer established by surgery
6 cases carcinoma cells, carcinoma
1 case carcinoma cells, cancer of uterus
Incidence, 0.9% carcinoma

Each of the preceding facts focused our attention on the role of human smegma. Most investigators[8] previously had used horse smegma because of the difficulty in obtaining the human variety. An abundant human supply was found in the South Carolina State Mental Hospital.

A great amount of work has been done on cancer in lower animals, the results of which are being used in attempts to interpret cancer in the human. Because a cancer was produced in one species of animal does not prove that it can be similarly produced in another. Sugar and Levy[9] stated that the belief that carcinoma of the cervix can be caused by exposure to an unproved carcinogenic agent at infrequent intervals cannot be condoned.

Spontaneous cervical cancer in mice is a rarity. Collins[10] and his group were the first to produce carcinoma of the cervix with any regularity in the mouse with local application of carcinogens. Murphy[11] has also reported a high incidence of cervical cancer in mice using the known carcinogen, methylcholanthrene. Using single insertions of crude smegma with ligation of the vagina, Twombly[12] produced one cervical cancer in a group of 48 mice, 12 of which survived long enough to be evaluated.

It has been hypothesized that the bacterial content of smegma, particularly *Mycobacterium smegmatis,* might convert its cholesterol content into a carcinogen. Sobel and Plaut[13] found that *Myco. smegmatis* consumed cholesterol actively when this substance was in its solid phase or in solution as its succinate.

A chemical analysis of the residue of smegma after drying to constant weight over concentrated sulfuric acid is shown in Table II. At present the fractionation of raw smegma is being done by Dr. Ray Brown of the University of Wisconsin Cancer Research Hospital and the effects of each of these fractions studied in mice by the same methods employed in this study.

TABLE II. CHEMICAL ANALYSIS OF THE RESIDUE OF SMEGMA AFTER DRYING TO CONSTANT WEIGHT OVER CONCENTRATED SULFURIC ACID

CONSTITUENT	%	
Total lipids		28.4
Phospholipids (as lecithin)	0.8	
Cholesterol (free)	3.8	
Cholesterol esters	1.0	
Neutral fats	22.8	
Total fatty acids		22.4
Iodine number of fatty acids		41.3

Materials and Methods

Whole raw human smegma obtained by retraction of the foreskin and the evacuation of this material from about the glans in uncircumcised males has been of paramount importance in this experiment. The bacterial and chemical components of smegma, the bacterial flora of the female genital tract, ovarian dermoid cyst contents, and simple trauma and estrogens have also been investigated as corollary and control aspects of this problem. Two basic methods have been employed: the repeated application of these materials to the cervix and upper vagina of the mouse by means of a metal speculum and the injection of a single "dose" into the vagina followed by closure of the vaginal orifice with sutures. The metal speculum was used in conjunction with an applicator which has a cupped end holding 3 mg. of the material to be tested.

The whole raw smegma was collected in sterile normal saline, centrifuged, ground into a paste, and stored in stoppered bottles in the refrigerator.

Female mice of the dba-1 strain were used at ages ranging from 7 to 20 weeks in the different groups with the addition of one group of white mice of the Wistar strain. The dba-1 strain was selected for two reasons: (1) no spontaneous cervical cancer had been reported in it, and (2) there was a known incidence of hereditary breast carcinoma in the strain. It was felt desirable to use animals which were not completely refractory to neoplastic disease.

Results

The results in the various groups are summarized in Tables III and IV. Mice were deleted from final pathological evaluation if postmortem changes were extreme, if the animals had been partially devoured by cage mates, or if death occurred within a few days after they were committed to the experiment. Animals were not sacrificed unless obviously and seriously diseased, as it was believed rational to expose them to the various agents for as long a period of time as possible.

TABLE III. SUMMARY OF EXPERIMENTAL RESULTS

GROUP	METHOD	MICE INJECTED	SUITABLE FOR EVALUATION	TUMORS
1.	Weekly vaginal injection of smegma	41	26	0
2.	Biweekly vaginal injection of smegma	15	12	6
3.	Introduction of smegma with vaginal ligation	54	25	4
4.	Introduction of smegma with vaginal ligation and injection of estrogen weekly	12	12	1
5.	Introduction of smegma with vaginal ligation and biweekly injection of increasing amounts of estrogen	14	4	0
6.	Weekly vaginal injection of smegma and injection of estrogen weekly	10	6	0
7.	Simple ligation of vagina without smegma	12	10	0
8.	Introduction of sterile smegma with vaginal ligation	13	6	0
9.	Introduction of ovarian dermoid-cyst contents with vaginal ligation	14	12	2
10.	Biweekly vaginal injection of dermoid-cyst contents	17	11	0
11.	Injection of smegma into artificial skin tunnels	15	4	0
12.	Biweekly vaginal injection of culture of 100% *Myco. smegmatis*	14	6	0
13.	Biweekly injection of mixed bacterial culture corresponding to bacteriological analysis of smegma including 10% *Myco. smegmatis*	35	27	1
14.	Biweekly injections of 100% *Myco. smegmatis* in culture with 5% cholesterol	25	16	0
15.	Biweekly vaginal injection of 0.3% methylcholanthrene in coconut oil	20	16	1
16.	Biweekly vaginal injections of 0.5% methylcholanthrene in lard	10	10	1
17.	Insertion of clean speculum and obturator	30	21	0
18.	Raw smegma biweekly vaginal injections	50	25	1
19.	Human vaginal culture	23	19	0
20.	White mice (Wistar strain), raw smegma biweekly	10	6	0

TABLE IV. SUMMARY OF RAW SMEGMA GROUPS

Total No. of dba-1 mice used for injection and ligation		160
No. suitable for final evaluation		88
Results.—		
Epidermoid carcinoma	8	
Sarcoma	2	
Malignant papilloma	1	
Marked hyperplasia	22	

After the impressive results found in Group 2 (the biweekly injection of raw smegma), this experiment was repeated. It was begun in May, 1956, on 50 animals (Group 18), of which only 6 remain alive at present (19 died early in study of "pneumonia"). Of the 25 available for study, there was no epithelial change in 7, mild to marked hyperplasia in 17, and one cancer of the cervix (Fig. 1). This tumor was in a mouse after 13¾ months of exposure to 118 injections.

In the groups of 88 mice in which whole raw smegma has been used by either the injection or ligation techniques, there have been 8 epidermoid carcinomas or an incidence of 10.2 per cent. If hyperplastic changes are included there are significant changes in 35.2 per cent (exclusive of the sarcomas). It is probable that many of the lesions placed in the hyperplastic category could have justifiably been classified as intraepithelial carcinoma (Figs. 2 and 3). In a detailed histological study of induced cervical carcinoma in the mouse, Scarpelli and von Haam[14] produced 139 malignant lesions

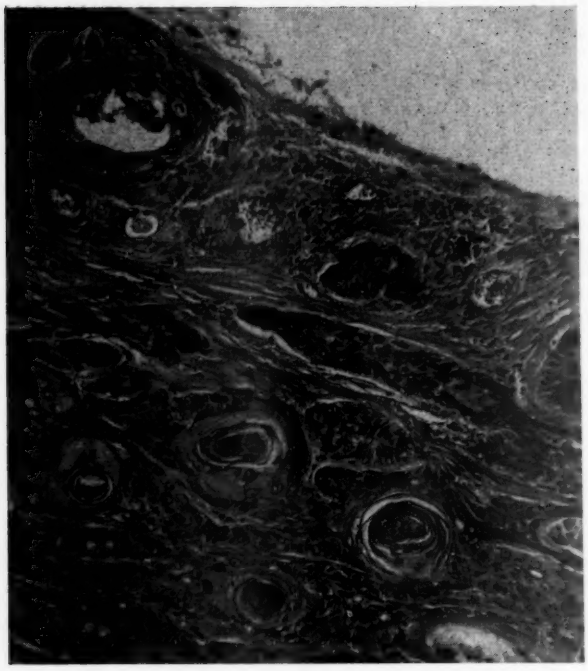

Fig. 1.—Squamous-cell carcinoma produced by applications of smegma biweekly for 14 months. (Hematoxylin and eosin. ×250; reduced ⅕.)

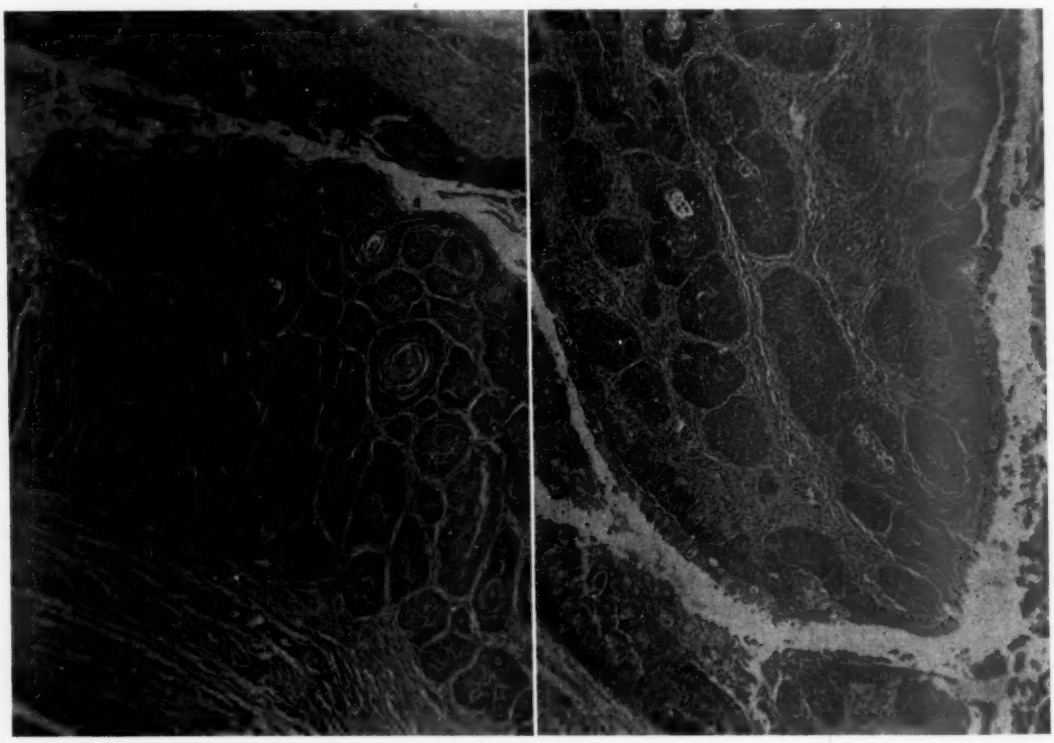

Fig. 2. Fig. 3.

Fig. 2.—Marked epithelial hyperplasia in mouse receiving applications of 100 per cent *Myco. smegmatis* with 5 per cent cholesterol biweekly for 9 months. (Hematoxylin and eosin. ×85; reduced ⅕.)

Fig. 3.—Illustration of the type of epithelial hyperplasia which was very difficult if not impossible to distinguish from intraepithelial carcinoma. (Hematoxylin and eosin: ×85; reduced ⅕.)

in 261 C_3H mice, using either 3,4 benzpyrene or 20-methylcholanthrene. They classified these neoplasms as invasive in 72 animals and noninvasive in 67. It appears from study of their description and illustrations that we produced many lesions comparable to their noninvasive carcinomas. Indeed we have been impressed with the difficulty in differentiating between various stages of atypical hyperplasia and carcinoma, but in an experiment dealing with the testing of a material of unknown carcinogenic potency, we choose to err on the conservative side and to classify borderline states as hyperplasia.

In Group 17, in which the clean speculum and obturator were simply repeatedly introduced into the vagina, no carcinoma developed. Two mice had marked hyperplasia of the cervicovaginal mucosa after 20 months (163 introductions).

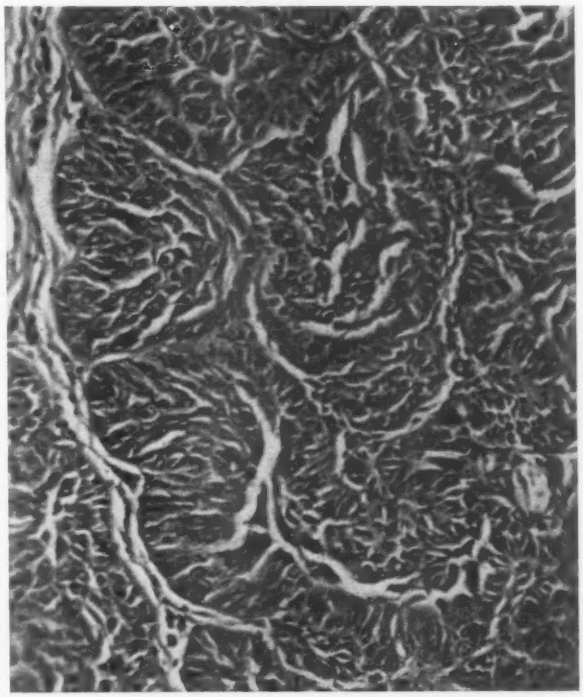

Fig. 4.—Marked epithelial hyperplasia with convoluted and reduplicated nests of cells. (Hematoxylin and eosin. ×250; reduced ⅙.)

The various groups (12, 13, 14, 19) in which bacteria were used supplied interesting results in all cases in which *Myco. smegmatis* was a component.

In Group 12, with 100 per cent *Myco. smegmatis* culture used biweekly, no invasive carcinomas were encountered, but 8 mice died almost immediately and 2 of the remaining animals exhibited intense epithelial hyperplasia (Fig. 4) after 10 months (63 injections) and 11 months (70 injections), respectively. These changes most probably represented carcinomatous transformation, but as they could not definitely be proved they were not designated as such.

In Group 13, in which mixed bacterial cultures were used corresponding to analysis of smegma and including 10 per cent *Myco. smegmatis,* there were even more pronounced results. One invasive carcinoma was found after 21½ months (141 injections). Two other mice showed intense hyperplasia, one with papilloma after 14¾ months (95 injections). These hyperplastic states were indistinguishable from intraepithelial carcinoma.

No carcinoma was found in Group 14 but in one case profound epithelial hyperplasia occurred at the end of 14 months (114 injections).

Cultures of the vagina were obtained from 25 patients and the bacterial flora analyzed as to the type of organism and per cent. An artificial culture was then recreated which had the following composition: *Staphylococcus albus* 40 per cent, *Staphylococcus aureus* 10 per cent, *Escherichia coli* 10 per cent, *Aerobacter aerogenes* 10 per cent, diptheroids 10 per cent, and Lactobacilli sp. 20 per cent. No carcinomas resulted and the hyperplastic changes were not as marked as those noted in the other groups. There was marked hyperplasia in one animal after 9½ months and 73 injections. This material proved to be quite lethal for the mice and it was difficult to keep them alive for a satisfactory length of time.

Biweekly injection of raw smegma into another strain of mouse in Group 20 did not produce carcinoma. There was one example of marked hyperplasia after 12½ months (104 injections). One animal is still alive.

Comment

The clinical and sociological facts and observations concerning smegma strongly indicate that in some way it is implicated in the genesis of penile and cervical carcinoma. Whole smegma as well as some of its components is stimulatory to the cervicovaginal epithelium of mice and invasive carcinoma will eventuate if the stimulus persists. It must be realized that the epithelium of the lower genital tract of mice is labile and probably reacts proliferatively to a wide variety of stimuli. Whole raw smegma, however, exclusive of known carcinogens, has proved to be the most effective stimulus in this experiment, followed by either some of its components or closely allied substances.

If lack of circumcision should prove to be of significance in the development of cervical cancer, a gradual reduction of this type of cancer may be expected in the United States. Wynder[2] has noted the circumcision rate in groups of hospitals studied to be 80 to 85 per cent of the non-Jewish males.

As Younge[15] has recently stressed, celibacy and late marriage will never be popular methods of the control of cervical cancer. He enthusiastically feels that invasive cancer of the cervix can be prevented by widespread advocation of circumcision, care of the abnormal-appearing cervix, and early detection of intraepithelial cancer.

Epidermoid cancer of the cervix has been noted in women exposed only to circumcised males and in virgins. Other etiological factors than those involving coitus and lack of circumcision must therefore exist.

Conclusions

1. The circumstanial evidence of the relationship between carcinoma of the cervix in women and smegma has been discussed.

2. In dba-1 strain mice, cancer of the cervix can be produced by human smegma, if this stimulus is continued for 14 months or more.

The objections to the use of lower animals in reference to human cancer are obvious. A similar study with the use of an experimental animal of primate level is contemplated.

The technical assistance of Miss Ann Clark and Mr. Frank Wyman is gratefully acknowledged.

We also wish to thank Frank Cordle of the Department of Microbiology and Robert Brown and Ethel McMinn of the Department of Medical Illustration for their cooperation.

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Discussion

DR. F. BAYARD CARTER, Durham, N. C.—The authors certainly prove in the dba-1 strain mice that cancer can be produced by human smegma, if this stimulus is continued for 14 months or more.

The bacteriologic studies would be of great interest since the virus theory of human cancer is ever with us. The theory also that trichomoniasis causes epithelial changes which may proceed to noninvasive or to invasive cancer is also prevalent.

The awakening of pathologists to the changes which can take place in the cervical epithelium has led to many interesting speculations concerning the stimulus or stimuli which initiate these changes. As clinicians we are all interested in these changes. Most of us would hope in discussing a paper of this type to bring to it greater knowledge than we possess.

DR. FRANK R. SMITH, New York, N. Y.—We have made a clinical study of racial incidence, in an effort to find some etiological factor for carcinoma of the cervix. We found, of course, that it was very rare in Jewish women. One factor that we suspected was the use of Lysol douches. Of course, I did not realize at the time that this popular douche material was probably much more commonly used by women who had cancer than in the control groups, but the reason was that the women who had cancer had leukorrhea and needed a so-called cleansing douche more often.

However, in studying that problem we took Rhesus monkeys and applied Lysol to the cervix three times a week for about 2½ years. A biopsy of the cervix was made every 3 months. When the war interrupted my work the monkeys were destroyed and some of the records were lost.

Of course, if you take Lysol stronger than 10% you get a burn. It is a burn with a subsequent reaction in the cervix, just like any other ulcerative burn. If you take 1 or 2 per cent Lysol, however, and apply it on a tampon which is changed three times a week, you can get a different change from what you get where merely a foreign body like cotton or boric acid or soda bicarbonate, the common douche materials, are used.

At the end of the 2½ years we had many of these metaplasias. We had the beginning of what is now called carcinoma in situ.

The work that should have been done in keeping with that study was bacterological study, but I did not have the setup to check the bacteria of the vagina.

All the clinical evidence points to smegma as a factor in the causation of cancer of the cervix. But it seems to me that there must be some factor other than just the smegma. There must be some component either the excess of, or the lack of which, makes one individual who is almost identical with others, get cancer, and a great many not. Carcinoma of the cervix is considered a disease of poverty and multiparity. When you think of the Jewish people as being quite prolific and of the Italian people as also being quite prolific, yet the first has a low incidence and the second has a very high incidence of cancer of the cervix, it makes you feel that the factor of smegma must play a part.

DR. J. ERNEST AYRE, Miami, Fla.—Dr. Hein and co-workers provide impressive evidence that human smegma acts as a carcinogenic agent when applied to the vagina and cervix of the dba mouse at repeated intervals. The evidence is convincing that smegma does have carcinogenic properties. Undoubtedly, as they have suggested, there are other environmental factors and possibly other carcinogens, some as yet unknown, which enter into the production of epidermoid cancer of the cervix. It appears that smegma and its bacterial constituents set up an inflammatory lesion which precedes the development of extreme hyperplasia and later epidermoid carcinoma. It is difficult to know where the role of smegma ends in the production of cancer. It has been our observation that other forms of infection and chronic inflammation may also contribute in a significant way to the development of cervical cancer. It has been our belief that most cancer is preceded by inflammation, whether of gonorrheal or nonspecific type, to which the cervix may be subjected repeatedly whenever pregnancy, miscarriage, or abortion ensues. The Mycobacterium of smegma probably represents only one of the infectious or inflammatory agents exerting carcinogenic effects upon cervical cells.

I would like to discuss some of the circumstantial evidence which throws some light upon the role played by such infections. First, vaginal or cervical discharge according to Hausdorff is so common as to have been described as a causative cancer factor and we have personally observed that women who exhibit chronic cervicitis with precancerous cell changes, receiving large continuous doses of potent estrogens, may develop papillomas of the vulva where the excessive outpouring of cervical mucus constantly bathes the skin. This provides suggestive evidence that the mucus from the cervix contains growth-promoting factors. Second, skenitis, which most commonly arises from gonorrheal infection, is present in a considerable proportion of women in whom routine cervical cytology reveals precancerous or in situ lesions. In research cytologic studies at the Miami Cancer Institute it was shown that cancer is three times as common in charity gynecologic clinic groups of women exhibiting a high proportion of chronic pelvic inflammatory disease and/or menometrorrhagia, as compared to patients who attend the offices of private physicians.

It has been shown by Institute workers too that in the City of Miami Department of Health Venereal Disease Clinics almost four times as much cancer of the cervix was found as compared to findings in private patients. Cervical cancer is *more common in sterile married women* than in unmarried women. The inference is that whenever Skene's ducts or the Fallopian tubes or the Bartholin gland or other parts of the femal genital tract are involved with gonorrheal infection, the cervix almost invariably have been similarly involved. And the character of the racemose glands of the endocervix is such as to render them susceptible to blockage and protracted inflammation. Undoubtedly in many cases the conditioning of the tissues by the infection or inflammation precedes the appearance of embryonic cancer cells by several years.

It has been shown that cancer of the cervix is 60 per cent more common in the Negro than in the white and in the latter group the incidence increases among women in the lower income brackets.

In contrast to the well-documented statistical evidence of the increased incidence of cervical cancer with early coitus and with multiple partners (divorcees) at the other extreme, it has been shown that among nuns cervical cancer is practically nonexistent. It is my contention that this absence of cancer arises because of the total absence of sex-borne infections and chronic inflammations.

DR. HEINS (Closing).—In answer to Dr. Ayre, about *Mycobacterium smegmatis* in alkaline scretions from the cervix, we have not done any work on this as yet.

There must be a quantitative difference of the carcinogenic agent, whether bacterial or chemical, in various batches of smegma. Some batches certainly vary in physical appearance. We have reported what we found. It is very easy to get enthusiastic about some facet of this whole multifaceted problem. We are certainly not pounding the drum, trying to "sell" smegma as the answer to the etiology of carcinoma of the cervix. We get definite invasive cancer of the cervix before it is reported as such. The portion of the material that is carcinogenic, if any, is what we have got to find.

As regards dermoid cyst contents, we thought at the beginning that it might be interesting to try to compare it, as a control, with smegma, since it also occurs in an enclosed skinlike surface and is originally sterile. However, we could not keep it sterile to use it as an absolute control.

As to the use of an experimental animal of as low a level as the mouse, you have to start somewhere. We are looking forward to getting a colony of monkeys. We are going to duplicate the experiment with these monkeys and we are also trying to get a group of women, such as in a prison in Columbia, South Carolina, to whose cervices we can apply this material under controlled conditions, following them with smears and biopsies.

COMPLICATIONS OF HYSTEROSALPINGOGRAPHY*

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IN THE last few years, hysterosalpingography has become the most effective procedure used in our efforts to help the sterile woman. The procedure is therapeutic as well as diagnostic. All of us who have been interested in sterility are familiar with the disappointments and limitations of hormones, enzymic agents, surgery, and psychiatry. As a matter of fact, the interest of the gynecologist is being more and more directed to the Fallopian tubes as the most fruitful and important point of attack. The patency or occlusion of the Fallopian tubes must be determined once the fundamentals of conception, namely, the presence of spermatozoa and of ovulation, have been established.

The purposes of hysterosalpingography are: (1) to diagnose patency or occlusion of the Fallopian tube, (2) to diagnose pathological conditions of the uterus and tubes, (3) to evaluate the extent of tubal occlusion and the site of tubal occlusion preparatory to salpingostomy, (4) to act as a therapeutic agent in overcoming tubal occlusion.

This paper is concerned with the complications we have encountered in 500 consecutive hysterograms in private white patients.

Technique

The technique used is a simplified one which requires no hospitalization, no anesthesia, and no preliminary preparation. The time we pick for the procedure is between days 10 and 13 after the onset of menstruation. We use surgically clean instruments and gloves and freshly laundered sheets for draping. The patient does not eat for 4 or more hours prior to the study. She is requested to empty her bladder before entering the x-ray room for study.

If the patient has had preliminary hysterogram studies a simple preliminary film is made of the pelvis. She is placed in the lithotomy position on an x-ray table equipped with Bucky diaphragm, her legs draped comfortably and suspended in stirrups.

A preliminary bimanual examination is made to determine the position of the uterus and to check for anatomical abnormalities. A speculum is then inserted and the cervix and vaginal vault are cleansed with a 5 per cent aqueous solution of Mercurochrome. A tenaculum is placed on the anterior lip of the cervix and a probe is then inserted through the cervix to determine once again the position and direction of the cervical canal and uterus.

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A sterile syringe containing a radiopaque medium is attached to a cervical cannula and all air bubbles in the cannula and syringe are expressed. The cannula tip is then inserted in the cervical canal so that the adjustable rubber acorn fits snugly at the external os when counterpressure is made with the tenaculum.

Two to three centimeters of the opaque medium is injected slowly and the first film is made. This film is processed and examined immediately. Further injections and subsequent films are then made as required. We have found it valuable to repeat the films after every 2 or 3 c.c. of dye is injected and to take between 15 and 20 minutes for the procedure. The amount of dye required varies considerably from 3 or 4 up to as much as 20 c.c., depending upon the size of the cervix and uterus and tubes. The average amount used is approximately 7 to 10 c.c.

Delayed films are not routinely necessary as the cannula is kept in place until all films have been developed and read.

No manometers are used. The complaints and condition of the patient during the procedure are indicative of whether or not excessive pressure is being exerted. Since the patient is not under anesthesia, there is little danger of rupturing a Fallopian tube before she complains of pain. There has been no case of rupture of a tube in our experience.

The ideal radiopaque medium for hysterosalpingography has yet to be discovered. Iodochlorol,* an iodized peanut oil, was used in a large majority of cases in this series. We have used most of the newer water-soluble media but have found them no safer nor any more free from complications than the oil media. We do not feel that the criticism of entrapping oil in old hydrosalpinx or the occasional oil granuloma is sufficient argument for discontinuing the use of iodized oils. It is our feeling that a tube whose lining epithelium is damaged by longstanding infection will probably absorb neither water-soluble material nor oil and that one will cause little more damage than the other.

The main reason, however, for using heavy iodized oil is the therapeutic value we believe it has in overcoming mild degrees of tubal obstruction. This may be because the weight of the medium exerts a prolonged pressure on the fimbriated end of the pendant tube. Increased viscosity prevents ready escape of oil from the tubes and aids in expanding the tubes and possibly separating agglutinated linings of the tubes. Prolonged pressure on points of obstruction or spasm is maintained by the technique of maintaining pressure during the interval while each film is developed and read before additional oil is injected.

Complications

The complications encountered during and following the procedures were: (1) pain, (2) a shocklike syndrome, (3) pelvic infection, (4) bleeding, and (5) intravasation of the material into the venous sinuses. These complications are set forth in Tables I to V.

To list "pain" as a complication is, of course, open to question because of the difficulty in evaluating pain. The degree of discomfort tolerated without complaining varies tremendously from one patient to another. Apprehension, psychic factors, and variation of the pain threshold all influence the patient's reaction to stimuli and this reaction cannot be accurately recorded. We have recorded pain as a complication, however, when the patient's complaints of discomfort warrant concern on the part of the physician.

*G. D. Searle & Company.

TABLE I. INCIDENCE OF PAIN

	NO.		%
During the Procedure.—	6		1.2
Severe (procedure discontinued)		3	
Moderate (procedure completed)		3	
Delayed.—	8		1.6
24 hours or less		6	
1 day to 14 days		2	
Total	14		2.8

Pain has not been a frequent complication but in 3 cases the patient complained of such severe pain that the procedure was discontinued. In these cases in which the pain threshold is extremely low or, for some unexplained reason, the procedure is unusually painful, we discontinue it and advise hospitalization and anesthesia for the procedure. Three other patients found the procedure very painful but were willing to permit us to continue until the completion of the study. Mild discomfort was a frequent complaint. Eight patients complained of pain in the pelvis following the procedure. Six of these had pain that lasted less than 24 hours while 2 stated that their pain lasted for several days. These patients were temporarily incapacitated but required only bed rest and symptomatic therapy.

TABLE II. INCIDENCE OF SHOCKLIKE SYNDROME

	NO.	%
Nausea, vomiting, sweating	2	
Fainting	5	
Convulsions	2	
Total	9	1.8

The shocklike state that has been observed in 9 of these patients is interesting and not explained. Two of these patients became clammy, cold, perspired profusely, and experienced nausea and vomiting. Five lost consciousness and 2 had mild convulsive seizures. In each case when this complication occurred the procedure was discontinued immediately, the patient was placed in Trendelenburg position, and cold packs were applied to the face and forehead. This was all the treatment required and all responded and were able to return to their homes within an hour after the procedure. Some of these patients volunteered the information that at menstruation they vomited and felt faint.

TABLE III. INCIDENCE OF INFECTION

	NO.	%
Pelvic infections	5	1

We feel that the number of cases of salpingitis or pelvic peritonitis following this procedure is low because the patients are, to some degree, selected, being private white patients. One patient in the group did not complain for about 5 days following the procedure, then had a temperature of 103° F., and was hospitalized in a neighboring town for about 15 days. She responded to chemotherapy and bed rest. This particular case may or may not be a true complication of hysterosalpingography alone because she had had a Rubin test one month prior to her hysterogram. Since this incident, we seldom invade the uterine cavity without waiting at least 2 months before another attempt at opening the tubes.

One patient developed a large left adnexal mass following the procedure. This patient had been hospitalized for curettage and anterior and posterior plastic repair. The hysterogram was done prior to the operation and it is questionable whether the complication should be attributed to the hysterogram itself. It seems inadvisable to do gynecological surgery and hysterosalpingography at the same time.

The other 3 patients had temperatures of 101° to 102° F. and were also treated with chemotherapy and bed rest, but their convalescence took only a a few days.

Most infections following hysterosalpingography are probably flare-ups of existing infection rather than a direct result of the procedure. Some of the symptoms attributed to infection may be allergic reactions to the medium used or sterile or chemical peritonitis. The most severe pelvic peritonitis that we have encountered has been following a Rubin test and we have had one ruptured tube in attempting a Rubin test. It has been our experience, therefore, that serious infectious complications are more likely with the Rubin test than with hysterosalpingography.

TABLE IV. INCIDENCE OF BLEEDING

	NO.	%
Profuse (menorrhagia) 2 weeks later	1	
Slight	2	
Total	3	0.6

Bleeding is not a serious complication. Only 2 patients had slight bleeding for the day following the procedure, which cleared up spontaneously. The other patient reported a frank hemorrhage about 2 weeks after her hysterogram. This was in conjunction with a period but, since the patient did not have a history of menorrhagia, it was attributed to the procedure.

TABLE V. INCIDENCE OF INTRAVASATION

	NO.	%
Intravasation (venogram)	6	1.2

Most of the cases of intravasation were simply the outlining of the venous sinuses and occasionally the uterine veins. We think the extremely low incidence of this complication is due to the fact that we inject very small amounts of oil at a time and view the film before injecting further amounts of oil. In this way we can discontinue the procedure before significant amounts of oil have entered the venous system. In 2 of these cases we have had chest x-rays without demonstrating any oil deposited in the lung fields. When first encountered, this complication was rather alarming but we are convinced that it is relatively innocuous if it is recognized early and the procedure discontinued. These patients have required no treatment. Another reason the incidence is so low is that the procedure is done in all cases from the tenth to the thirteenth day of the menstrual cycle when the vascularity of the uterus is minimal. When the complication did occur it did not seem commensurate with the pressure applied.

It has been difficult to diagnose uterotubal spasm as such and it is not listed as a complication. In some cases of bilateral closure, uterotubal spasm has probably been a factor. However, we have not used relaxants or anesthesia or other therapy directed specifically to overcoming uterotubal spasm.

Diagnostic and Therapeutic Results

While this paper does not encompass the field of therapeutic results or diagnoses made, I believe it is worth while to mention a few observations (Table VI).

TABLE VI. X-RAY DIAGNOSIS

	NO.	%
Bilateral closed tubes	58	11.6
Patent tubes, unilateral or bilateral	442	88.4
Uterus didelphys or subseptus	6	1.2
Hydrosalpinx	21	4.2
Infantile uterus	4	0.8
Submucous fibroid	9	1.8

It is important that gynecologists do their own hysterosalpingograms because there is so much information which cannot be obtained by reading an x-ray film or the radiologist's interpretation. It has been our experience that the radiologists seem to read more in the film than actually is present. For instance, 71 cases showed unilateral closure of the tube; however, this had very little significance as many of these tubes were visualized out to the fimbriated extremity with spillage from the opposite tube. It was felt that, rather than deposit a large amount of dye in the pelvis through the readily patent tube, it is better to discontinue after one tube is proved to be open and the other completely visualized. A delayed film will often prove the patency of both tubes.

For the purpose of evaluating the therapeutic effect of hysterosalpingography as far as pregnancy is concerned, we have attributed pregnancy to the procedure if it follows within 90 days. In this series, 88 pregnancies, or 17.6 per cent, occurred within 3 months. When this result is evaluated in the light of the 58 cases in which bilateral tubal occlusion was present and the large number of couples who were handicapped by aspermia or oligospermia, the therapeutic value of this procedure is striking.

Summary

1. The complications experienced in 500 consecutive hysterosalpingograms performed on private white patients have been listed and commented upon.

2. There was no death and very little morbidity in the series.

3. If precautions are taken to perform the procedure when the patient's stomach is empty, when there is no known pelvic infection present, and to discontinue the procedure upon the first signs of serious complications, it is safe and desirable in the study of sterility.

Discussion

DR. J. C. MOORE, Greenville, S. C.—It has been my practice to use the Rubin test as a screening test for tubal obstructions early in my fertility work-ups. Needless to say this is not a comparable test but I have seen no complications in using carbon dioxide. Many patients are followed up with hysterograms, but others conceive without this being necessary.

Dr. Woltz's reason for not giving anesthesia is certainly important. I use Trilene for analgesia for hysterograms. This seems to be appreciated by the patient and I have not observed that it increases the danger of rupture of the tubes.

It has been my practice to inject the dye under fluoroscopy control, thereby avoiding excess of dye in the peritoneal cavity. I feel that I have been fortunate to miss intravascular injection, which possibly would not be detected under flouroscopy.

In contrast to Dr. Woltz, I use water-soluble dyes exclusively, believing them to be safer. During the past 3 to 4 years I have used Salpix. I have always used a screw-type Hudgins cannula, but I readily see why an acorn attachment would cause less discomfort. The author commented that pain during this procedure was difficult to evaluate. I have felt that endocervical dilatation and pressure caused considerable pain. In my practice I have not observed any complications that resemble a shocklike syndrome. I have no proved explanation for this complication, but believe that some patients will go into shock from pain. Anaphylactic-type reactions are a possible cause. The convulsions may be related to hypotensive reactions of cerebral anoxia. The only complications that I have personally observed are one infection and one apparent allergic reaction with peritoneal irritation for 48 hours. This latter case responded well to an antihistamine drug and oral cortisone.

Marshak, in his review of 2,500 cases of hysterography noted pain in 80 per cent of the cases, but only in cases where the dye entered the peritoneal cavity. In his series he used oil and water-soluble dye. He observed some chemical peritonitis with adhesions and possible granulomatous inflammation. He reported 300 cases of embolism in his series in which Lipiodol was used. Extremely rare fatal emboli are known to occur. Marshak believed that there was no danger of embolic phenomena with the water-soluble dye, but he expressed the opinion that any dye can cause exacerbation of the chronic infection. He noted intravascular visualization in 38 of the 2,500 cases and in all of these the water-soluble dye was used; no emboli resulted.

Steinberg recently reported this experience with Ethiodol. He reminded us that Lipiodol would take months to absorb from the peritoneal cavity and that foreign-body granulomatous formation may result. This author agreed that water-soluble dye would not cause pulmonary emboli, but would cause considerable cramp-like pain on contact with the peritoneum. It was his opinion that the latter was not observed with oil media. Steinberg believed that the absorption of the water-soluble media after 15 to 20 minutes was a disadvantage because of the importance of a 24 hour film. Ethiodol was used in 161 cases; the absorption time lies between that of water-soluble dye and of Lipiodol. Steinberg further felt that the oil media were contraindicated in case of abortion or curettage less than 6 weeks previously, and in cases of intermenstrual bleeding because of the increased possibility of intravascular injection.

Bergman reported that foreign-body granulomatous formations may also result from a water-soluble agent. Garzon observed 3 cases of intravascular injection and related this to tuberculosis of the endometrium.

It would be interesting and informative to see a controlled series of hysterograms comparing the complications of an oil medium against those of a water-soluble dye, and the therapeutic advantage of each.

VARIATIONS IN THE PERIPHERAL CIRCULATION DURING PREGNANCY*†

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THE purpose of this investigation was to determine the pattern of changes that occur in the flow and distribution of blood to the extremities during normal pregnancy, and to identify the factors predominantly influencing these variations.

Material and Methods

Over 5,660 determinations were made on the peripheral circulation of 58 normal pregnant subjects by means of: (1) the venous occlusion plethysmokymograph, (2) the measurement of skin temperatures by a modified potentiometric method, and (3) digital plethysmograms. The results were compared with values obtained under identical environmental conditions in 3,750 determinations on the peripheral circulation of a carefully selected control group of 25 normal nongravid women.

Results

In the control group, the over-all average resting forearm blood flow was 4.56 ± 0.10 c.c. per minute per 100 c.c. of tissue, and the average finger skin temperature was 34.2 ± 0.35° C. The average resting leg blood flow was 1.87 ± 0.10 c.c. per minute per 100 c.c. of tissue, and the average toe skin temperature was 29.1 ± 0.55° C. No correlation could be found between the daily variations observed in the peripheral circulation and hormonal cycles associated with menstruation.

Under identical conditions of investigation, a consistent, uniform pattern of changes was observed in the peripheral circulation during normal pregnancy. No studies were made prior to the twelfth week of gestation. From that time until the twentieth week of gestation, however, blood flow to both the upper and lower extremities was found to be less than that observed in nonpregnant individuals. In the period from 20 to 24 weeks of gestation there was evidence of a remarkable increase in peripheral blood flow, as values obtained rose well above the level found in the control group of nongravid women. From 24 to 36

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‡The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

weeks of gestation a steady, progressive increase in blood flow and skin temperatures was noted in all extremities. In the thirty-sixth and thirty-seventh weeks of pregnancy the maximal peripheral circulatory adjustments occurred. The average resting forearm blood flow reached a value of 8.73 ± 0.48 c.c. per minute per 100 c.c. of tissue, representing a 91 per cent increase over the control level. The average finger skin temperature rose to 35.9 ± 0.04° C. Simultaneously, blood flow to the lower extremities increased 70 per cent to an average value of 3.18 ± 0.29 c.c. per minute per 100 c.c. of tissue, and the average toe skin temperatures rose to 31.7 ± 0.54° C. These average values obtained during the period of maximal circulatory adjustment in pregnancy were nearly twice as great as the averages observed in the nongravid control group. From the thirty-eighth week of gestation until term, there was evidence of a moderate, gradual decrease in the peripheral circulation to all extremities. In the postpartum period, prior to ambulation, despite the fact that the major portion of the uterine circulation had been occluded, no significant changes were observed in the average blood flow values and average skin temperatures in both the upper and lower extremities. Following ambulation, however, there was evidence of a marked decrease in peripheral blood flow, and within 6 to 10 weeks after parturition the values for blood flow and skin temperature were found to have returned to control levels. Analysis of the data disclosed no significant difference between the variations observed in primigravid and multigravid women.

The pattern of alterations observed in the peripheral circulation during normal pregnancy appeared to be closely associated with known systemic cardiovascular adjustments in gestation. A positive correlation was established between changes in the peripheral circulation and reported variations in cardiac output, total blood and plasma volumes, and the velocity of blood flow. An inverse relationship was found between peripheral circulatory variations and reported changes in blood viscosity, circulation times, and hematocrit values.

No correlation could be established between the pattern of changes in the peripheral circulation and known excretion levels of hormones considered essential to successful gestation. This was interpreted as evidence that hormonal factors play a minor role in the peripheral cardiovascular adjustments in normal pregnancy.

In an attempt to demonstrate alterations in vasomotor activity, photographic records of digital pulsations were made on all subjects. Digital plethysmograms thus obtained were employed for qualitative analysis of the amplitude of pulsations. In the control group of nongravid women, no consistent variations were noted during the various phases of the menstrual cycle. Although greater individual variations were noted in average values recorded during normal pregnancy, the general trend of changes closely followed the previously determined circulatory pattern; that is, concomitant with the increase in the volume of blood flow to the extremities, there was an increase of about equal magnitude in the pulse amplitude of the digits. In a study of the fluctuations noted in the digital pulse amplitudes of each subject during each test period, however, the range of values obtained showed progressively greater variations throughout the development of pregnancy. Maximal variations in the photographically recorded digital pulsations of each individual occurred at term. Such variations were interpreted as evidence of an increasing lability of the vasomotor system during gestation.

A definite mechanical effect of the enlarging gravid uterus upon peripheral blood flow was demonstrated by comparison of values obtained with the venous

occlusion plethysmokymograph from the upper extremities with those observed in the lower extremities. Two types of alterations were noted:

1. In 8 cases the fixation of the fetal head deep in the maternal pelvis caused a *decrease* in blood flow to the legs, while forearm blood flow continued to *increase* steadily during pregnancy. In all other subjects, when fixation of the fetal head was not noted, changes in the peripheral circulation to *both* the upper and lower extremities were parallel and qualitatively similar.

2. In 12 cases gross fetal movements resulting in changes in the obstetrical position or presentation of the fetus within the gravid uterus caused marked alterations in the resting blood flow to the lower extremities, while simultaneously no change could be observed in blood flow to the upper extremities. No measurable effect on the peripheral circulation was observed from the usual "kicking" motions frequently visible and palpable in the abdomen of the pregnant woman.

These mechanical effects demonstrated in the circulation to the lower extremities presumably were due to alterations in the pressure exerted by the presenting part of the fetus on the great vessels traversing the maternal pelvis.

As a result of an unusual degree of cooperation on the part of 2 primigravid test subjects, successful determinations of blood flow, skin temperature, and pulse amplitude were made during the first stage of active labor. Some rather remarkable and consistent changes in the peripheral circulation to both the upper and lower extremities were observed and seem worthy of note. A transitory peripheral vasoconstriction was observed with the initiation of each uterine contraction. This phenomenon preceded the conscious perception of pain by a brief interval, and continued throughout the period of contraction. Vasodilatation, with an increase in peripheral blood flow, occurred concurrently with relaxation of the uterine musculature.

Summary

1. A large series of determinations made with three different methods of evaluating peripheral blood flow demonstrate a progressive increase in the peripheral circulation during the development of normal pregnancy.

2. A definite mechanical effect of the enlarging gravid uterus on blood flow to the lower extremities was demonstrated coincidentally with the fixation of the fetal head deep in the maternal pelvis, and during gross fetal movements.

3. Within 6 to 10 weeks following delivery values observed in the peripheral circulation had returned to prepregnancy levels.

Discussion

DR. FRANK R. LOCK, Winston-Salem, N. C.—Dr. Herbert has chosen a field of investigation that has received little attention in this country. It has been a subject of much speculation and few facts. Raynaud's observation that peripheral vasospastic disease was relieved by pregnancy was prophetic. It was apparently overlooked by Huchart, who, in 1910, postulated that peripheral vasoconstriction in pregnancy was the rule. Numerous theories to explain this postulate were presented before sound research exploded the myth. Abramson and his associates in 1943 and Burt in 1949, employing different techniques, reached the same conclusion that peripheral blood flow increases during pregnancy. How many times have we asked why the palms of the hands are red during pregnancy? Present and previous studies help us to understand this.

Dr. Herbert and his associates have determined peripheral circulation in pregnancy through three acceptable, indirect, concurrent techniques. Control values have been carefully established. Frequent sequential determinations suggest changes which have been previously unrecognized. Blood flow to the liver, brain, and kidney remains essentially unchanged in pregnancy, while flow through the uterus increases. Normal flow to the extremities would be expected as a further manifestation of the human body's ability to maintain homeostasis. Why then is the peripheral circulation increased? An increase in metabolic and muscular work requires increased heat dissipation which would result from increased cutaneous circulation. This popular explanation, unfortunately, remains unproved. Dr. Herbert has mentioned the increased lability of the vasomotor system during pregnancy. He has stated that the observations were made under identical environmental conditions for all subjects, but he has not specified whether basal conditions were present for all determinations. It is recognized that temperature, anxiety, or nervousness markedly increases the sympathetic outflow. Abrupt reductions in digital pulse waves result. To imply that peripheral vasoconstriction observed with uterine contractions is initially independent of conscious perception as a cause for increased sympathetic tone is premature at the present.

DR. HERBERT (Closing).—Let me make just one final point in closing.

Dr. Lock, in regard to the term "basal conditions," I purposely avoided using this specific terminology in my discussion. I think that by the time you get any woman into all the apparatus that is required to be applied to her for these studies, it is difficult for anyone to certify that she is in a basal state. We did, however, conscientiously attempt to simulate as closely as we could ideal "basal conditions." For example, constant temperature and humidity of the test room were maintained throughout the series of examinations; the subjects were each given a full hour of complete bed rest following the application of all apparatus before any blood flow determinations were made; a single investigator conducted all tests; silence was maintained during the rest and test periods, no food had been ingested for at least 4 to 6 hours prior to the measurements; and external stimuli of any type were scrupulously avoided in the test situation. In fact, many of the subjects fell asleep before any tests were run at all.

Despite all these precautions, the determinations were made with the full realization that with all the apparatus applied to them, we could not assume the subjects were in an ideal "basal state." We did try to compensate for this, in part, however, by running a very large number of tests.

PREGNANCY IN THE YOUNG PRIMIGRAVIDA*

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A DEFINITE trend toward childbearing at an earlier age has been indicated by the reports of the National Office of Vital Statistics. Relatively few studies of the complications of pregnancy and delivery in the young primigravida have been reported in recent years. The present study was undertaken to evaluate the problem in the light of current obstetric practice.

Material

The young primigravida is defined for this study as a woman who has her first delivery at 15 years of age or younger. The records of 299 young primigravidas were reviewed. They were delivered at Grady Memorial Hospital under the supervision of the Department of Obstetrics and Gynecology of the Emory University School of Medicine. Eighty-three of the patients were white (27.8 per cent) and 216 were Negro. The deliveries occurred between 1949 and 1953. The young primigravidas constituted 1.2 per cent of the white patients and 2.5 per cent of the Negro patients delivered during the period of this study. All deliveries at Grady Memorial Hospital are service cases. The patients reported upon in this study are being followed so that in a later survey the complications which develop in subsequent pregnancies may be evaluated.

The age distribution and marital status at delivery are shown in Table I. The percentage of the Negro women under 15 years of age was 33.8 and of the white 21.6. Seventy and four tenths per cent of the Negro patients and 15.7 per cent of the white patients stated that they were not married.

TABLE I. AGE DISTRIBUTION AND MARITAL STATUS

	WHITE	NEGRO
Age.—		
15 years	65	143
14 years	16	61
13 years	2	9
12 years	0	3
Marital Status.—		
Married	70	64
Single	13	152

Antepartal Care

Antepartal care was received by 265 patients (75 white and 190 Negro). Nineteen patients, all Negro, registered for antepartal care but did not return

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until labor had begun. Thus 53 patients (17.7 per cent) may be considered as not having received antepartal care. Only 20 of the latter were married.

The stage of gestation at which the patients were first seen and their marital status are shown in Table II. It should be noted that 67.9 per cent of the patients seen in the first trimester were married, while only 42.1 per cent and 40.3 per cent of those seen first in the second and third trimesters were married. Of those seen for the first time in labor, 70.6 per cent stated that they were single.

TABLE II. STAGE OF PREGNANCY WHEN THE PATIENT WAS FIRST SEEN

	WHITE				NEGRO			
			ANTEPARTAL CARE				ANTEPARTAL CARE	
STAGE OF PREGNANCY	MARRIED	SINGLE	ADEQUATE	INADEQUATE	MARRIED	SINGLE	ADEQUATE	INADEQUATE
First trimester	23	1	22	2	13	16	22	7
Second trimester	30	3	21	12	31	81	59	53
Third trimester	12	6	7	11	15	34	10	39
Labor	5	3	0	8	5	21	0	26
Total	70	13	50	33	64	152	91	125

The adequacy of antepartal care was appraised on the basis of: (1) the stage of pregnancy at which the patient was first seen, (2) the number of antepartal visits made, and (3) the regularity with which the patients attended the clinics. The care was judged inadequate if the patient was not seen until the last month of pregnancy, if she made less than four visits, and if she skipped more than three appointments in succession.

The antepartal care was considered adequate in 141 cases; 74 of these patients were married. The care was judged to be inadequate in 158 cases; 98, or 62.0 per cent, of these patients were unmarried (Table III).

TABLE III. ADEQUACY OF ANTEPARTAL CARE

	WHITE		NEGRO		
CARE	MARRIED	SINGLE	MARRIED	SINGLE	TOTAL
Adequate	47	3	27	64	141
Inadequate	23	10	37	88	158
Total	70	13	64	152	299

TABLE IV. TOXEMIA

	RACE		MARITAL STATUS		ANTEPARTAL CARE	
TOXEMIA	WHITE	NEGRO	MARRIED	SINGLE	ADEQUATE	INADEQUATE
Mild pre-eclampsia	8	31	13	26	14	25
Severe pre-eclampsia	3	9	6	6	6	6
Eclampsia	0	2	1	1	0	2
Total	11	42	20	33	20	33

Toxemia

The acute toxemias of pregnancy were the most common major obstetrical complication (Table IV). They occurred in 53 patients (17.7 per cent). The incidence of toxemia was 13.3 per cent among the white patients and 19.4 per

cent among the Negro. The marital status of the patients with toxemia was given as 20 married (37.7 per cent) and 33 single (62.3 per cent). The toxemia was classified as mild pre-eclampsia in 39, severe pre-eclampsia in 12, and eclampsia in 2.

The 39 cases of mild pre-eclampsia included 25 patients who had received inadequate antepartal care. In only 5 cases were the patients admitted to the hospital and labor induced primarily because of mild pre-eclampsia. The other cases were first diagnosed at the time the patients were admitted in labor. Mild pre-eclampsia was diagnosed in 32 patients at term.

Adequate antepartal care had been received by only 6 of the 12 patients with severe pre-eclampsia. Four of the 6 who received adequate care were admitted to the hospital for induction of labor.

The 2 cases of eclampsia occurred in Negro patients who had received no antepartal care. Both patients had their first convulsion at home and were in labor when admitted to the hospital. The pregnancy was at term in one case and at 30 weeks in the other. Both infants were stillborn.

Other Complications

Syphilis.—This disease was diagnosed in 15 patients, none of whom were married. The syphilis was classified as early latent in 12, secondary in 1, and congenital in 2. Treatment was given to 14 of these patients during pregnancy. The disease was diagnosed at delivery in one patient who had not received antepartal care.

There was a past record of syphilis in 4 other single Negro patients. All of these had received adequate therapy and did not show any evidence of disease.

Rheumatic Heart Disease.—Rheumatic heart disease was diagnosed in 4 patients, none of whom gave a history of cardiac decompensation. From a cardiac standpoint, all did well in pregnancy, labor, and delivery. There was a history of rheumatic fever in 4 other patients who showed no signs of cardiac involvement.

Abortions.—Abortion occurred in 12 patients, in the first trimester in 10 and in the second trimester in 2. All denied criminal induction of the abortion.

Antepartal Bleeding.—There were 4 cases of antepartal bleeding. These were diagnosed as rupture of the marginal sinus in 2 cases and partial abruptio placentae in 2 cases. The abruptio placentae occurred at term in one case in association with eclampsia and at approximately 28 weeks in the other.

Miscellaneous.—Nausea and vomiting was sufficiently severe to warrant hospitalization in only one case. Psychiatric treatment was given to one patient. This patient had received psychiatric therapy prior to her pregnancy and it was continued during and after the pregnancy. Only one patient was classified as mentally deficient.

The other medical diseases complicating pregnancy were one case of inactive pulmonary tuberculosis, one case of juvenile diabetes, and one case of thyrotoxicosis. Treatment of the latter patient consisted of antithyroid drugs and subtotal thyroidectomy during pregnancy. There was one diagnosed case of acute gonorrhea and one case of gonorrheal arthritis. One patient suffered a poisonous snake bite; this case was complicated by thrombophlebitis of the involved extremity.

One patient had a ruptured cornual pregnancy complicated by chorioadenoma destruens. The patient was alive and apparently well 3 years later.

Labor

Labor was prolonged over 24 hours in 13 cases, an incidence of 4.4 per cent. The second stage of labor was longer than 1 hour in 8 patients. Sedation was given as the cause of the prolonged second stage in 2 cases and the occiput posterior position in 6. One retained placenta was the only abnormality of the third stage. There were no cases of postpartum hemorrhage.

Cephalic presentation occurred in 283 cases and breech presentation in 4. Of the latter, 3 were at term and one the second of premature twins. There was one transverse presentation.

Labor was induced in 9 patients. The indication in all cases was acute toxemia, and all inductions were successful on the first attempt.

There were 5 deliveries by indicated low forceps and 6 by midforceps. A posterior position was the indication for 5 of the midforceps applications and transverse arrest for one. Three cesarean sections of the low cervical type were performed. The indication for one was diabetes and toxemia; the indication for the other 2 was a contracted pelvis.

Postpartum Morbidity

An abnormal elevation of temperature was recorded in 19 cases, a postpartum morbidity rate of 6.4 per cent. Endometritis was the cause of the temperature elevation in 14 cases, breast abscess in one, and pyelonephritis in 4. A breakdown of the episiotomy occurred in one patient who also had endometritis.

Infants

There were 288 infants delivered, including one set of twins. Of these, 238 weighed 2,500 grams or over and 50 (17.4 per cent) weighed less than 2,500 grams. There were 10 neonatal deaths (3.5 per cent) and 7 stillbirths (2.4 per cent), giving a perinatal mortality rate of 5.9 per cent (Table V).

TABLE V. INFANTS

	NO. OF INFANTS		NEONATAL DEATHS		STILLBIRTHS	
	WHITE	NEGRO	WHITE	NEGRO	WHITE	NEGRO
Term	70	168	2	0	0	4
Premature	9	41	1	7	0	3
Total	79	209	3	7	0	7

Nine of the white patients (11.4 per cent) had premature infants, as compared with 41 (19.6 per cent) of the Negro patients. There were no stillbirths and 3 neonatal deaths among the white patients, a perinatal mortality rate of 3.8 per cent, compared with 7 stillbirths and 7 neonatal deaths among the Negro patients, a perinatal mortality rate of 6.7 per cent.

Six term infants died. Of these 2 were neonatal deaths and 4 stillbirths. Antepartal care was considered adequate in only one of these. There were no complicating factors in 4 (2 stillbirths and 2 neonatal deaths). Eclampsia and abruptio placentae complicated one stillbirth. The other occurred with a transverse presentation.

The weight distribution of the premature infants is shown in Table VI. It should be noted that 33 (6 white and 27 Negro) infants weighed between 2,000 and 2,499 grams. These were 66 per cent of all the prematures.

Only one white premature infant died. The mother had no antepartal care and suffered severe pre-eclampsia. Toxemia was associated with 4 premature

deaths among the Negroes. Labor was induced in all of these cases. Abruptio placentae was the cause of the stillbirth of one premature Negro infant. Another infant was stillborn whose mother had syphilis and had not received treatment. There were no complicating factors except prematurity in 4 of the perinatal deaths of Negro infants. All the deaths of premature infants occurred in cases with inadequate antepartal care.

TABLE VI. WEIGHT DISTRIBUTION OF PREMATURE INFANTS

WEIGHT	WHITE	NEGRO	STILLBORN	NEONATAL DEATH
2,000-2,499 grams	6	27	0	2
1,500-1,999 grams	1	8	1	2
1,000-1,499 grams	1	5	2	2
Less than 1,000 grams	1	1	0	2
Total	9	41	3	8

Comments

The age distribution of the two groups shows a difference only in that 21.6 per cent of the white patients and 33.8 per cent of the Negroes were under 15 years of age. The marital status of the two was more significantly different in that 84.3 per cent of the white and only 29.6 per cent of the Negro patients were married, in comparison with the general obstetrical ratio at Grady Memorial Hospital of 96 per cent white and 78 per cent Negro patients married at the time of their delivery.

The majority of both white and Negro patients sought care in the second trimester of pregnancy, as do most obstetrical patients at Grady Memorial Hospital. A significant fact was that although only 17.7 per cent of the patients were seen in the first trimester, 67.9 per cent of these were married. Even though white patients constituted 27.8 per cent of all patients, they accounted for 45.3 per cent of the patients seen in the first trimester.

Only 47.2 per cent of the patients received adequate antepartal care, in spite of adequate and easily accessible facilities. It is significant that 52.5 per cent of those who received adequate care were married and that 60.2 per cent of the white patients received adequate care, while only 42.1 per cent of the Negro patients did.

The incidence of acute toxemia was three times as great as that seen on the entire obstetrical service. It is well known that there is a higher incidence of toxemia among the Negroes in the South. This fact held true in this study with a 13.3 per cent incidence in the white and 19.4 per cent in the Negro. Only 37.7 per cent of the patients with toxemia were married and only 37.7 per cent received adequate care.

Nineteen patients either had syphilis or had a past record of the disease. It is surprising to see such a high incidence among such young patients. It is significant that all of these patients were Negroes and that 17 were not married.

The low incidence (4.0 per cent) of abortion may be explained by the fact that most patients who have abortions are treated in the Outpatient Department at Grady Memorial Hospital.

Labor and the puerperium presented no complications in the young primigravidas which could be attributed to the age of the patient. The operative rate compares favorably with that of the other obstetrical patients at Grady Memorial Hospital.

The study showed a high incidence of prematurity (17.4 per cent) and a high perinatal mortality rate (5.9 per cent) among the young primigravidas.

The rate for both was higher in the Negro patients. This holds true in the patients delivered at Grady Memorial Hospital. No completely satisfactory explanation can be given for the higher premature and perinatal mortality rates. The only correlating features are the lack of adequate antepartal care and the high incidence of toxemia among these patients.

The two conspicuous features disclosed in this survey are the high rate of unmarried patients and the lack of adequate antepartal care. The two are parallel and appear in greater frequency in the Negro patients. The frequency of complications was also greater in the patients who were not married and who did not receive adequate care.

This study points to the great need for sex education and education for parenthood at a relatively early age. It would seem advisable that such instruction be included in the curriculum of the school, in church study groups, and certainly in the home. From the medical standpoint, it should be noted that the ages of some of these patients reach back into the years when they are still under the care of the pediatrician. The guidance of the parent and the patient in sex education could be begun by the pediatrician.

Summary

A study of pregnancy and delivery has been made in 299 white and Negro women 15 years of age and younger. Fifteen and seven-tenths per cent of the white patients and 70.4 per cent of the Negro patients stated that they were not married. Antepartal care was considered adequate in only 47.2 per cent of the patients.

The acute toxemias of pregnancy, which occurred in 17.7 per cent of the patients, were the most common major obstetrical complication. Labor and delivery were not influenced by the age of the patient. The perinatal mortality rate was 5.9 per cent and the prematurity rate was 17.4 per cent.

The frequency of complications was greater in the patients who were not married and who did not receive adequate care. The need for sex education and education for parenthood at an early age is stressed.

Discussion

DR. JOHN M. NOKES, Charlottesville, Va.—Dr. Poliakoff brings to our attention again a pitiful social welfare problem for which there is no easy solution.

His article adds confirmatory evidence to the many fine studies published in the past two decades which, despite minor differences, are in general agreement that the young primigravida presents no unique problem from a strictly obstetric viewpoint. In fact, the weight of the data is to the contrary. The young primigravida appears to be in somewhat more favorable statistical circumstance than her older sister. Her labor tends to be as short or shorter, and freer from such complications as cephalopelvic disproportion, abruptio-placentae, and, of course, placenta previa. Thus, there is an almost unanimous reporting of a lower cesarean section rate in this group.

Furthermore, as documented information has accumulated, we have found that most of the apprehensions formerly held concerning the young primigravida were without fact or foundation. The birth weight of her child is close to the average figure. She does not show an increase in premature delivery, postpartum hemorrhage, puerperal morbidity, lacerations of the birth canal, or malpresentations of the fetus.

In addition, the outcome for her baby is not only as favorable as that of the average primigravida, but actually more so, inasmuch as most series report a decreased perinatal mortality in the young primigravida.

The high incidence of syphilis (19 cases) among such young patients should serve as a challenge to the Public Health authorities of the State of Georgia.

The young primigravida does differ from her older counterpart, although it is more a difference in degree than difference in kind. She tends to be unmarried and she tends to show an increase in toxemia, both in total incidence and in severity. The former is not usually taken to be within the province of the obstetrician while the latter is—yet they both undoubtedly have the same etiological background. It is almost automatic to associate an increase in toxemia with a decrease in antepartum care, yet reference to Table I will point out the fallacy of that belief. Dr. Poliakoff reports that 47 per cent of his patients received adequate prenatal care and that these patients presented a 17 per cent incidence of toxemia. Our paper reported an adequate prenatal program in only 31 per cent of patients with an 18 per cent incidence of toxemia. On the other hand, Sinclair (J. Obst. & Gynaec., Brit. Emp. 59:504, 1952), reported that 81 per cent of his patients received adequate prenatal care, Schmitz and Towne (Surg., Gynec. & Obst. 84:962, 1947) reported 85 per cent, and Marchetti and Menaker (AM. J. OBST. & GYNEC. 59: 1013, 1950) reported 95 per cent with reported incidences of toxemia of 16, 15, and 20 per cent, respectively.

TABLE I

AUTHOR	NUMBER PATIENTS	MAXIMUM AGE IN SERIES	PRE-ECLAMPSIA	ECLAMPSIA	ADEQUATE PRENATAL CARE	% NEGROES	CESAREAN SECTION RATE	POSTPARTUM HEMORRHAGE	PREMATURITY RATE	BABIES' WEIGHT	% CONGENITAL DEFECTS	LENGTH OF LABOR	PERINATAL LOSS
Sinclair	700	16	16.0%	3.3%	81%		↓	↓	S	S	S	↓	
Hofmeister and Burgess	136	15	11.7%			2%	↓	↑ Slt.	S		S		S
Schmitz and Towne	200	17	15.0%		85%	0	↓			S		↓	
Marchetti and Menaker	634	16	20.0%	5.6%	95%	99%	↓	↑ Slt.	↑ Slt.		S	↓	↓
Nokes and Thornton	894	17	18.0%	3.0%	31%	65%	↓			S		S	↓
Poliakoff	299	15	17.0%		47%	72%	S		↑				↑

↑, higher than average for entire service. ↓, lower than average for entire service. S, same as average for entire service.

So it cannot be the mere lack of prenatal care per se which is responsible for the increased toxemia rate in this group. It is well known that adolescents tend to disregard instructions and restrictions, and what is prenatal care if not "instructions and restrictions"? The high incidence of toxemia in the young primigravida will certainly hinder us in our efforts further to reduce maternal deaths from this cause.

The problem, therefore, of both toxemia and illegitimacy in this group can be reduced to the problem of education. Unfortunately, the development of emotional and intellectual maturity lags behind the development of biologic maturity. The problems of the young primigravida will not be solved by any advance in obstetric technique, but rather by an advance in our thinking and approach toward education in an effort to erase the disparity between intellectual and physiologic maturity.

DR. ARTHUR L. RIVERS, Charleston, S. C.—I would like to ask Dr. Poliakoff whether or not his group has had any success in using the relaxants in these patients with toxemia. I am ashamed to report that we had a case of eclampsia last week in a girl of 18 who had been in the office the previous Wednesday, and she had two convulsions on the

following Thursday. Her blood pressure was 135/85. After she had had two convulsions, the blood pressure was 160/120, and she had 3 plus albumin. The cervix was not as favorable as we would like for induction of labor, but we thought it was safe. The membranes were ruptured, and, after sedation and magnesium sulfates, we began intravenous Pitocin and Cervilaxin. We think we had some success in shortening her labor because she was delivered perfectly normally 7 hours later the same day after having had the Cervilaxin.

DR. HERBERT E. SCHMITZ, Chicago, Ill.—Several years ago we undertook a similar study involving 200 unwed youngsters. We have this material in St. Vincent's Infant and Maternity Hospital in Chicago, which is an institution for the care of unwed mothers. All of our patients were single.

We had complete control of this group because as soon as their problem is revealed to the social service department of the Catholic Charities of Chicago, they are sent to this home. From then on their diet and their complete control is within the institution and they have no chance of getting out or breaking away from the routine.

We also had an increased rate of toxemia. I doubt that the diet alone or the restriction of the individual plays a part.

We had no other complications. We had one cesarean section, which was for disproportion. In every instance labor was shortened in these individuals, and we had an over-all and uncorrected fetal loss of 4.5 per cent.

Our conclusions were exactly the same as those of Dr. Poliakoff, that these youngsters can go into labor, have very few complications and over-all have a much shorter and much easier labor than the average patient.

DR. POLIAKOFF (closing).—In answer to Dr. Rivers' question on the use of relaxing agents; they were not used. In general, the patients were delivered rapidly after the induction was begun.

EXPERIENCE WITH THE BRACHT METHOD OF DELIVERY OF THE BREECH*

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SINCE the review article by Albert A. Plentl and Raymond E. Stone[1] in the June, 1953, issue of *Obstetrical and Gynecological Survey*, we have endeavored to use the Bracht maneuver as described in that article whenever it was applicable. We feel that the method is a simple, safe method for both mother and baby, by which the great majority of mature live infants in the breech presentation may be delivered. Practically all the articles and descriptions of the Bracht maneuver are in the European and South American literature. Very few articles have appeared in the English, American, or Canadian journals, and I have been unable to find any mention of this method of delivery of a breech in the major American journals since publication of this review article. It is primarily because of this sparsity of mention in the literature, the lack of knowledge of the method by the practicing obstetricians in this country, and the ease, simplicity, and safety of the method that it is presented.

Our cases and per cent of success and failure are insignificant for evaluating the method, but it is our hope that this paper will stimulate interest in the method as a possible adjunct to the armamentarium in the management of breech.

Description of the Bracht Maneuver

As pointed out by Plentl and Stone (from whom this description is in most part taken), it is generally conceded that breech presentations have higher fetal mortality than vertex presentations. The chances of survival for babies presenting by breech decreased with the degree and time of interference. The more manipulation is performed and the earlier this manipulation is instituted, the greater are the fetal mortality and morbidity, to say nothing of the maternal injuries.

Without getting into the controversy of assisted breech versus early extraction, suffice it to say that all of the classical maneuvers consist primarily of downward traction and some form of rotation. Bracht, in his original description in 1936, and again in 1938, maintained that these classical maneuvers were being practiced because of widespread misunderstanding of the mechanism of labor in breeches. We have all been taught that the mechanism of labor in breech is similar, if not identical, to the mechanism of labor in vertex except that the polarity of the baby is reversed. This includes the various rotations of the pelvic girdle, shoulders, and head. Bracht pointed

*Presented at the Twentieth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hollywood, Florida, Feb. 1 to 5, 1958.

out that in a completely spontaneous delivery all of the force for delivery occurred from above, from uterine contractions and the abdominal muscles. All element of traction was absent. In spontaneous delivery the breech appears in the transverse position at the outlet. As labor progresses, the breech rotates slowly to the sacrum anterior position as the buttocks and trunk are delivered. Force applied from above produces a lordotic curvature in the baby, and its back lies against the mother's symphysis. The rotation around the symphysis continues upward, with the baby's trunk and shoulders in a transverse position in the pelvis, and the elbows, arms, and hands are delivered spontaneously. They are forced out by the aftercoming head. The neck is in extreme extension, the head in the anteroposterior position in the midpelvis with the face appearing at the outlet. The head is delivered spontaneously in the direct anteroposterior position.

Fig. 1.—Bracht maneuver: delivery of feet. Spontaneous delivery of breech to level of umbilicus. The baby's back is held upward against the mother's symphysis. After the feet pass over the perineum, gentle upward traction is continued. (From Plentl and Stone.[1])

Based upon these considerations, Bracht described the maneuver which he thought would stimulate the natural mechanism of delivery (Fig. 1). The breech is allowed to deliver spontaneously to the umbilicus without push or pull, the body and extended legs are held together with both hands, maintaining the upward and anterior rotation of the body. When the anterior rotation is nearly completed, the baby's body is held, not pressed, against the mother's symphysis. Force applied in this procedure should be equivalent to the force of gravity, that is, equivalent to the weight of that portion of the baby which has already been born. The mere maintenance of this position, added to the effects of uterine contractions and moderate suprapubic pressure by an assistant, suffices to complete the delivery by the spontaneous mechanism (Figs. 2 and 3). The delivery of the head is usually accomplished by moderate suprapubic pressure by an assistant and continuation of the attitude of extension with the baby held over the mother's symphysis. If this method fails, forceps may be used.

Plentl and Stone went into an extensive statistical analysis of the available reports and, because of the lack of specific information in some of the reports, the analysis left some doubt as to the absolute superiority of this method over the so-called classical methods. This paper is a report of our experiences with this method.

Material

The material consists of two groups of patients in three hospitals in Greenville, South Carolina (Table I). The first group was collected in a 30-month period at the Donaldson Air Force Base Hospital where one of us was stationed during part of this time. Thereafter we had control and supervision of the service as consultants. Of interest is the low cesarean section rate, 1.59 per cent. The other group consists of private practice patients from October, 1953, through December, 1957. These were scheduled private practice deliveries in two hospitals in Greenville, South Carolina: the Greenville General and St. Francis. Here there was a cesarean section rate of 2.71 per cent.

TABLE I. TOTAL NUMBER OF TERM DELIVERIES AND BREECH DELIVERIES IN BOTH DONALDSON AIR FORCE BASE AND PRIVATE PRACTICE GROUPS

GROUP 1 D.A.F.B.			GROUP 2 PRIVATE PRACTICE		
Deliveries	2,451		Deliveries	1,400	
Breech	61	2.44%	Breech	63	4.5%
Sections	39	1.59%	Sections	38	2.71%
Total deliveries		3,851			
Term breech deliveries		124		3.21%	
Sections (all causes)		77		1.84%	

On account of the impossibility of getting all the charts on the Air Force group of patients, the remainder of the report will be confined to the private practice group where all records were available. The composition of this group is outlined in Table II.

TABLE II. ANALYSIS OF THE PRIVATE PRACTICE GROUP

Total deliveries		1,400
Term breech deliveries		63
Primigravidas (27)		
Ages	15 to 33 years	
Duration of labor	2 to 24 hours	
Weight of babies	5 pounds, 8 ounces to 9 pounds, 6 ounces	
Multigravidas (36)		
Ages	18 to 44 years	
Duration of labor	3 to 17 hours	
Weight of babies	5 pounds, 8 ounces to 9 pounds, 1 ounce	
Presentations		
Frank and complete	51	80.9%
Double footling	8	12.7%
Single footling	4	6.4%

Pitocin was used to induce labor in 4 cases and to stimulate contractions in 12 others. Two babies were the second of twins and one was the second of triplets.

Sedation consisted of Nembutal, Demerol and scopolamine, alone or in combination with Thorazine or Sparine.* We believe that sedation in breech

*Sparine (promazine hydrochloride), trade-mark of Wyeth Laboratories, Philadelphia, Pa.

Fig. 2.—Bracht maneuver: delivery of arms and shoulders. The expulsive force transmitted by the baby's head results in simultaneous delivery of both elbows, followed by arms and finally the shoulders in transverse position. (From Plentl and Stone.[1])

Fig. 3.—Bracht maneuver: delivery of head. Continued maintenance of extreme extension. The head is delivered spontaneously in anteroposterior position. (From Plentl and Stone.[1])

presentations can be given in the same manner as in vertex presentation. Our usual sedation consists of 25 mg. Sparine intramuscularly, and 1½ grains Nembutal orally on admission to the hospital. Demerol, 100 mg., and scopolamine, 1/150 grain intramuscularly, are then given on request of the patient, and Demerol, 50 mg., and scopolamine, 1/150 grain, every 1 to 3 hours as needed. Sixty-two of these 63 patients received nitrous oxide and oxygen anesthesia. Twenty-five of them received a pudendal block also, and one patient received a pudendal block without gas. We do not use cyclopropane or ether before delivery of the baby. The largest amount of sedation received by any of these patients in this series occurred at the time when we were changing from Thorazine to Sparine and the patient inadvertently received Sparine, 50 mg., Nembutal, 3 grains, on admission, and Demeral, 100 mg., and scopolamine, 1/150 grain, twice. She was a gravida i, and had had a total of 11 hours of labor. This baby will be mentioned under the fetal complications.

Results

The Bracht maneuver (Table III) was used for complete delivery of the baby in 45 of these 63 cases. In these cases there was some manipulation but absolutely no rotation or traction. The Bracht maneuver was used for delivery of the baby up to the head, and forceps were applied to the head, in 13 cases, giving a total of 58 or 92 per cent of the cases which we classified as successful. There were 5 cases (8 per cent) which we classified as failures because we could not or elected not to use the Bracht maneuver. These cases were associated with extended arms (2 cases), prolapsed cord (2 cases), and a very short cord (1 case).

TABLE III. RESULTS OF THE USE OF THE BRACHT MANEUVER IN THE PRIVATE PRACTICE GROUP OF PATIENTS

Bracht maneuver			
Complete	45		
With forceps	13		
Successful		58	92%
Failed		5	8%
Total		63	
Condition of babies			
Good		60	95.3%
Fair		3	4.7%
		63	
Condition of mothers			
Lacerations			
Perineal		1°	2
		2°	2
		3°	1
Cervical			4
Postpartum hemorrhage			3

Condition of the Babies

Sixty of these sixty-three babies (95.3 per cent) were considered in good condition one minute after complete delivery. Three (4.7 per cent) were considered in fair condition as follows:

1. The cord was tightly wrapped around the neck three times, and the immediate respirations were sluggish. The baby was resuscitated with oxygen in a rockette and was discharged from the hospital in good condition.

2. This baby had a depression of the skull at birth which was elevated surgically 24 hours post partum. The baby was cyanotic during the first 3 minutes after birth. He was discharged from the hospital in good condition. At the last check-up, at 2½ years of age, the baby was perfectly normal.

3. The baby was sleepy and sluggish at birth but breathed and was resuscitated with oxygen and the rockette. This was the baby of the patient who inadvertently received what we considered to be, at least for this patient, an excessive amount of sedation. The baby was discharged from the hospital in good condition.

Condition of the Mothers

Fifty-five patients had episiotomies, either mediolateral or median; there was one third-degree extension. This was in a 44-year-old gravida iii, with an 8 pound, 3 ounce baby. Eight patients did not have episiotomies for various reasons. Two of these patients sustained first-degree perineal lacerations, and two sustained second-degree perineal lacerations. There were 4 cervical lacerations. All of these 4 patients received Pitocin drip during the late first and second stages of labor, and in all 4 cases forceps were used. The cervix of each of these patients was examined and all the lacerations were repaired. One of these patients had a serious postpartum hemorrhage.

There were 3 patients who had postpartum hemorrhages:

1. This patient was a 27-year-old primigravida with an 8 pound, 12 ounce baby. She sustained a deep posterior laceration of the cervix. The bleeding was immediate and profuse, producing deep shock. The laceration was extremely difficult to expose and repair, and before the repair was completed and the patient recovered from the shock, 3,500 c.c. of blood was given.

2. A 25-year-old gravida iii, with a 6 pound, 11 ounce baby, this patient had a 10 cm. fibroid in the fundus. The baby had a matching depression in the left parietal area of the skull which was elevated surgically. There was a moderate posterior laceration of the cervix; 500 c.c. of blood was given to replace the blood loss.

3. Hemorrhage in this case was due to retained placental fragments. The bleeding started one hour post partum; 1,500 c.c. of blood was necessary to combat shock and replace blood loss.

There was one case of severe pre-eclampsia, admitted 10 days before onset of labor. Labor was induced and she had no complications with the delivery.

There were no cesarean sections done with the primary indication of breech presentation.

There were also no external versions done in these cases.

Conclusion

In conclusion, this paper is presented as a plea for familiarity with this method of delivery of the breech which is safe for the mother and baby and successful in a large majority of cases. If this method is not successful, one can always revert to the so-called "classical maneuvers." Apparently, as obstetricians, most of us are satisfied with our method of handling the breech problem; however, statistics will show that, throughout the country, perinatal morbidity and mortality in breech presentation are approximately two to three times those of vertex.

Reference

1. Plentl, A. A., and Stone, R. E.: Obst. & Gynec. Surv. 8: 313, 1953.

Discussion

DR. WILLIAM S. GRIZZARD, Petersburg, Va.—We are all interested in lowering the maternal and fetal morbidity and mortality of breech deliveries. Dr. Bellew describes the Bracht maneuver as a simple and safe method of breech delivery in the majority of the cases of live births.

I would like to ask when the essayist decides whether or not the Bracht maneuver is applicable, or does he start all breech deliveries by the Bracht method? Also, when should the maneuver be classed as a failure and forceps applied?

The Bracht method appears to be simple to use. However, it is my feeling that the plane of anesthesia is a large factor in considering the successful termination of delivery by this method. Dr. Bellew pointed out that 62 of 63 cases reviewed were delivered under nitrous oxide and oxygen—no ether or cyclopropane. Pudendal block was also used in 25 cases. Therefore, the frequency, strength, and duration of the uterine contractions were not lessened by anesthesia. This in itself would be a valuable aid in successfully terminating the delivery of breech births by the Bracht method. Anesthesia with ether or cyclopropane and oxygen in sufficient amounts to allow an episiotomy to be done without pain would lessen the frequency, strength, and duration of the uterine contractions and ultimately decrease the number of successful deliveries by this method.

I would like to ask if the suprapubic pressure is produced by a physician or by a nurse. Also I would like to ask how the essayist maintains control of the fetal head to prevent its too rapid delivery over the perineum. It is our feeling that a sudden delivery with immediate release of pressure on the fetal skull predisposes to tentorial tears, also to perineal lacerations. How do you prevent overextension of the fetal neck?

Our method of breech deliveries is somewhat similar in that we encourage spontaneous delivery of the breech to the umbilicus. If the arms are extended or nuchal we use traction and rotation to deliver them; then a finger is inserted in the fetal mouth—this serves to maintain an airway and to guide the fetal head through the pelvis. The baby straddles the forearm and is raised up against the mother's symphysis. This allows a free hand to apply controlled suprapubic pressure. If the delivery is not accomplished easily in this manner, the fetus is held in the above-mentioned position by the circulating nurse and Piper forceps are applied to deliver the aftercoming head.

DR. BELLEW (Closing).—In regard to Dr. Grizzard's question concerning the cases on which we use the Bracht method, I would like to say that since we have become interested in this maneuver we try it first on all breech presentations. If it does not work, or if the case does not progress normally, we resort to the so-called "classic maneuver."

In regard to his second question as to when we apply forceps, we do not consider the necessity of applying forceps to the aftercoming head as a failure of the Bracht method. If the head cannot be delivered easily with slight suprapubic pressure, then we apply forceps.

In regard to his third question in which he asked if the individual applying the suprapubic pressure is always a physician, we certainly prefer it. We have interns or residents who are usually available, but not always, in which case the pressure is applied by a nurse.

In closing, I would like to say that the most amazing thing about the use of this procedure is the ease with which the whole delivery ordinarily takes place, including delivery of the head. As I stated in the paper, the usual cause of failure was not difficulty in delivering the head, but an extended arm, a prolapsed cord, or an extremely short cord.

SPONTANEOUS PREMATURE RUPTURE OF THE MEMBRANES*†

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LAST year there was presented to this Association the first report of the cooperative Perinatal Mortality Study which is being conducted by the Departments of Obstetrics and Gynecology of the University of North Carolina, Duke University, Bowman Gray School of Medicine, the School of Public Health of the University of North Carolina, and the North Carolina State Board of Health. This paper[1] emphasized the primary importance of socioeconomic factors in perinatal mortality and indicated that a sizable number of perinatal deaths were associated with spontaneous premature rupture of the membranes. A further study of this problem was thus stimulated.

Method of Study

The data for this study were obtained from the three cooperating medical schools and are based upon 7,511 deliveries of infants weighing 400 grams and above, which occurred between 1954 and 1956. The tabulations are taken from 763 study schedules based upon interviews and hospital records of single births with known birth weight and known latent period in the cases of spontaneous premature rupture of the membranes before the onset of clinical labor. In each tabulation of a given item, the unknowns have been excluded from the total.

The study schedule is a 6 page booklet plus a supplement for recording autopsy findings. Information for the schedule is obtained from the hospital records and by direct interview with the mother. A study schedule is prepared for all fetal and neonatal deaths occurring in the three University hospitals. A comparison study schedule is also completed for approximately every fifteenth infant who survives the neonatal period. The comparison group is selected in such a manner that the obstetrician is not aware of which infants will serve as controls until after delivery. Perinatal mortality in this study refers to all deaths of infants weighing 400 grams or more through the twenty-eighth day of life.

The statistical methods employed in the study have been reported by Wells, Greenberg, and Donnelly.[2]

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Incidence

The reported incidence of premature rupture of the membranes varies widely according to geographic locations. Di Guglielmo and Pepe[3] reported an incidence of 5 per cent in Argentina, while Embrey[4] reported 13.9 per cent in England and Kjessler[5] 18.9 per cent in Gothenburg, Sweden. In the United States, Cron and Brown[6] have reported an incidence of premature rupture of the membranes of 9 per cent while Eastman[7] has reported 12 per cent and Calkins[8] 14 per cent.

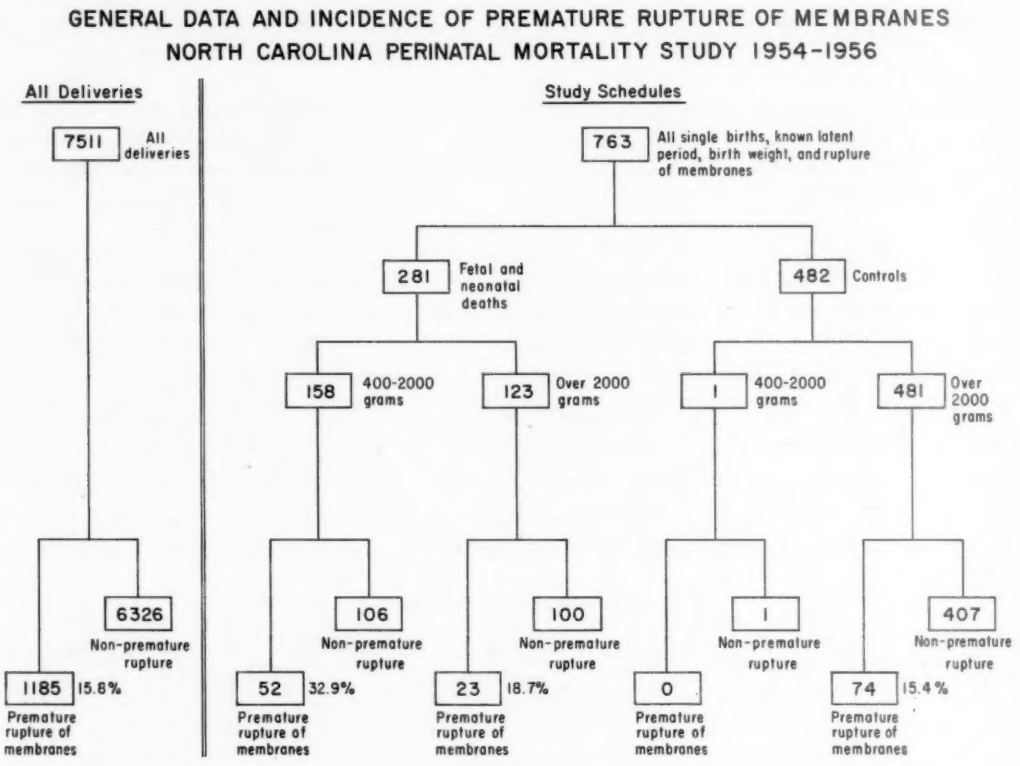

Fig. 1.

Fig. 1 depicts the incidence and importance of premature rupture of membranes in this study. The over-all incidence among the deliveries in the three medical schools was 15.8 per cent. However, 75, or 26.7 per cent of all the fetal and neonatal deaths, were associated with premature rupture of the membranes. This complication occurred in association with the birth of 32.9 per cent of the infants who weighed 400 to 2,000 grams and 18.7 per cent of those who weighed 2,001 grams and above.

Concurrent Obstetrical Complications

A study of the 52 deaths of infants weighing 400 to 2,000 grams and the 23 deaths of those weighing 2,001 grams and above with premature rupture of the membranes disclosed a sizable number of other major obstetrical complications (Table I).

These obstetrical complications assume added significance when they are converted into percentages of occurrence. Of the 75 fetal and neonatal deaths,

there were 24, or 32 per cent, complicated by infection. There were 20 mothers, or 26.7 per cent, in the same group who had premature separation of the placenta, rupture of the marginal sinus, or other significant antepartum bleeding. Approximately one half of these hemorrhagic complications, however, occurred in mothers whose infants weighed 400 to 1,000 grams. Eighteen, or 24 per cent, of all cases of fetal and neonatal death with premature rupture of the membranes were complicated by toxemia of pregnancy. The umbilical cord prolapsed in 16, or 21.3 per cent of all the cases, but this complication was responsible for the death of the infant in only 10.7 per cent of these 16 cases. Intrauterine death had occurred in the other cases prior to prolapse of the cord.

TABLE I. MAJOR OBSTETRICAL COMPLICATIONS ASSOCIATED WITH PREMATURE RUPTURE OF THE MEMBRANES

COMPLICATION	INFANTS 400-2,000 GRAMS		INFANTS 2,000 GRAMS AND ABOVE	
Antepartum or intrapartum fever above 99° F.	18		6	
Premature separation of the placenta, rupture of the marginal sinus, or other significant antepartum bleeding occurring before premature rupture of the membranes	12		3	
Premature separation of the placenta, rupture of the marginal sinus, or other significant antepartum bleeding occurring after premature rupture of the membranes	5		0	
Toxemia of pregnancy	7		11	
Prolapse of the umbilical cord	11		5	
Congenital anomalies incompatible with life	3		5	
Idiopathic fetal death in utero preceding rupture of the membranes	2		4	
Circumvallate placenta	4		0	
Diabetes	0		3	
Polyhydramnios	0		3	
Uterine inertia	0		3	
Abnormal presentations	20		7	
Breech		16		5
Face or Brow		2		1
Transverse Lie		2		1
Total fetal and neonatal deaths in cases of premature rupture of membranes	52		23	

The total is less than the sum in each column because of multiple complications

Abnormal presentations were associated with 27, or 36 per cent, of the total deaths in cases of premature rupture of the membranes. This complication was also associated with other lethal obstetrical conditions and contributed to a death rate of 31.82 per 100 deliveries of infants weighing 2,001 grams and above. This is shown in Table II where it is seen that the death rate in a similar weight group with obstetrical complications was only 4.26 per 100 deliveries when the membranes had not ruptured prematurely.

TABLE II. DEATH RATE PER 100 DELIVERIES OF INFANTS WEIGHING 2,001 GRAMS AND ABOVE ACCORDING TO PRESENTATION

	NO PREMATURE RUPTURE OF MEMBRANES	PREMATURE RUPTURE OF MEMBRANES
Total	1.74	2.03
Vertex	1.58	1.44
All others	4.26	31.82

Death rates in this and all other tables are computed by the following equation:

$$\text{Estimated perinatal mortality rate per 100 deliveries} = \frac{\text{Number of fetal and neonatal deaths} \times 100}{\text{Number of fetal and neonatal deaths} + \text{estimated number of survivors}}$$

Role of Premature Rupture of the Membranes in Perinatal Mortality

Since there was a high incidence of obstetrical complications associated with premature rupture of the membranes, each case was studied to determine whether rupture of the membranes was the major or initiating cause of death.

TABLE III. CASES IN WHICH PREMATURE RUPTURE OF THE MEMBRANES WAS NOT THE MAJOR OR INITIATING FACTOR IN PERINATAL DEATH

CAUSE OF DEATH	INFANTS 400-2,000 GRAMS	INFANTS 2,001 GRAMS AND ABOVE
Premature separation of the placenta, rupture of the marginal sinus, or significant antepartum bleeding occurring before rupture of the membranes	12	3
Congenital anomalies incompatible with life	3	5
Idiopathic fetal death in utero occurring before premature rupture of the membranes	2	3
Intrauterine anoxia associated with severe toxemia of pregnancy	2	3
Improper management of maternal diabetes	0	2
Maternal cardiac failure (membranes ruptured spontaneously after mother had developed severe failure)	2	0
Total	21	16
Total fetal and neonatal deaths in cases of premature rupture of membranes	52	23

It is evident from Table III that premature rupture of the membranes was not a major factor in the death of 21, or 40.4 per cent, of the infants weighing 400 to 2,000 grams and in 16, or 69.6 per cent, of the infants weighing 2,001 grams and above. Premature rupture of the membranes was merely an incidental occurrence. The infants actually succumbed to other lethal obstetrical complications such as premature separation of the placenta, toxemia of pregnancy, maternal diabetes, heart disease, congenital anomalies incompatible with life, and to idiopathic fetal death in utero occurring before rupture of the membranes.

TABLE IV. CASES IN WHICH PREMATURE RUPTURE OF THE MEMBRANES WAS THE POSSIBLE MAJOR OR INITIATING FACTOR IN PERINATAL MORTALITY

CAUSE OF DEATH	INFANTS 400-2,000 GRAMS	INFANTS 2,001 GRAMS AND ABOVE
Neonatal deaths associated with amnionitis, atelectasis, and/or hyaline membranes	11	1
Intrauterine deaths associated with amnionitis and/or intrauterine pneumonia	7	4
Prolapse of the umbilical cord (primary cause of death)	6	2
Premature separation of the placenta after premature rupture of the membranes	5	0
Intracranial hemorrhage (labor initiated by premature rupture of the membranes)	2	0
Total	31	7
Total fetal and neonatal deaths in cases of premature rupture of membranes	52	23

A review of the 75 deaths also showed that 31, or 59.6 per cent, of the infants weighing 400 to 2,000 grams, and 7, or 30.4 per cent, of the infants weighing 2,001 grams and above were possibly lost as a result of premature rupture of the membranes.

Intrauterine Infection, Latent Period, and the Duration of Labor

Intrauterine infection was the major cause of death in the cases in which the perinatal mortality was related to premature rupture of the membranes.

The membranes are an effective barrier to intrauterine infection; but when rupture occurs, bacteria invade the amniotic sac in a matter of hours. Once severe amnionitis is present, it may cause the demise of the infant from intrauterine pneumonia or contribute to pneumonia and atelectasis in the neonatal period. Moreover, the association of premature rupture of the membranes, fever, intrauterine anoxia, or other major obstetrical complications will increase the amount of aspiration of the amniotic contents and increase the likelihood of pulmonary infection.

Amnionitis and intrapartum infection contributed to 23, or 30.7 per cent, of the 75 deaths associated with premature rupture of the membranes. It cannot be stated that amnionitis or intrapartum infection was the real cause of death of the infants weighing less than 2,000 grams; prematurity alone could have been the lethal factor. But premature rupture of the membranes and a prolonged latent period were undoubtedly major factors in the 5 deaths of the larger infants.

Guilbeau and Eastman[7] have carefully evaluated the effect of the latent period on perinatal mortality in cases of premature rupture of the membranes. They have concluded that the duration of the latent period is not a significant factor in infants below 2,499 grams because of the major significance of prematurity. In mature infants, however, a latent period of 48 hours and greater is associated with a threefold increase in perinatal mortality.

The number of cases in this series is small compared to that of Guilbeau and Eastman, but there is a close correlation in the findings.

Table V shows the percentage of infants with various latent periods according to weight.

TABLE V. LATENT PERIOD IN CASES OF PREMATURE RUPTURE OF THE MEMBRANES

BIRTH WEIGHT (GRAMS)	TOTAL NO.	0-11 HOURS (%)	12-35 HOURS (%)	OVER 35 HOURS (%)
Perinatal Deaths.—				
400-2,000	52	15.4	17.3	67.3
2,001 and above	23	52.2	26.1	21.7
Survivors (Controls).—				
400-2,000	0			
2,001 and above	74	73.0	20.3	6.7

Only 32.7 per cent of the mothers who were delivered of infants in the lower weight group had a latent period of less than 35 hours. The average latent period in the cases in which the infant died in this weight group was 9 days.

Essentially 90 per cent of the 97 infants with premature rupture of the membranes who weighed 2,001 grams and above had latent periods of 35 hours and less. The latent period was longer than 36 hours in all cases of infants in this weight group with premature rupture of the membranes who died of amnionitis or intrapartum infection; in fact, 2 had latent periods of 38 hours, one of 6 days, one of 7 days, and one of 9 days.

In the weight group over 2,000 grams, the mothers of surviving infants had, on the average, a shorter latent period than the mothers of infants who did not survive.

The duration of labor in cases of premature rupture of the membranes is of less importance than the latent period but is of equal interest. Calkins[8] has stated that premature rupture of the membranes results in a reduction in the duration of labor.

Table VI gives a computation of the mean hours of labor in cases of fetal and neonatal death and of surviving infants with or without spontaneous premature rupture of the membranes.

TABLE VI. MEAN HOURS OF LABOR IN CASES OF FETAL AND NEONATAL DEATH AND SURVIVING INFANTS WITH AND WITHOUT SPONTANEOUS PREMATURE RUPTURE OF MEMBRANES

	NO PREMATURE RUPTURE OF MEMBRANES	PREMATURE RUPTURE OF MEMBRANES
Fetal and neonatal deaths		
400 to 2,000 grams	9.1	8.6
2,001 grams and above	10.7	16.8
Surviving infants		
2,001 grams and above	8.9	7.4

In the cases of surviving infants who weigh 2,001 grams and above there actually appears to be a reduction in the mean duration of labor with premature rupture of the membranes. But the mean duration of labor is increased for all infants in this weight group who died, and is almost doubled with premature rupture of the membranes. Thus premature rupture of the membranes has a favorable effect on the duration of labor only in surviving infants.

Prolapse of the Umbilical Cord

Of the 75 deaths studied in Table IV there were 8 deaths, or 10.7 per cent, which were possibly the result of prolapse of the umbilical cord in association with premature rupture of the membranes. All of these infants had some abnormality of presentation, either footling breech, transverse lie, or floating vertex. These deaths might have occurred if the membranes had ruptured during labors not complicated by premature rupture of the membranes but whether or not in this magnitude is not known. The data concerning prolapse of the cord are included for completeness. It is difficult, with the paucity of data, to determine its absolute significance in the problem of spontaneous premature rupture of membranes.

Errors in the Management of Cases of Premature Rupture of the Membranes

It is possible to criticize the obstetrical management of some cases in any series of perinatal deaths, particularly when the deaths are associated with a number of major obstetrical complications. This series is no exception. There were 18, or 24 per cent, in which there were thought to be errors in obstetrical management (Table VII). Only 8, or 10.7 per cent, of these cases were unquestionably associated with the problem of premature rupture of the membranes.

Delivery of the breech was poorly and unskillfully managed in the case of one infant weighing 1,600 grams and of another infant weighing 3,800 grams. Cesarean section would have been preferable to version and extraction in the case of a 2,700 gram infant with a latent period of 36 hours and a transverse lie. There were 3 cases of maternal diabetes the management of which are open to criticism. One infant weighing 1,700 grams died as a result of totally inadequate care by the referring physician. Two other mothers with breech presentations of infants weighing 2,800 and 3,800 grams should probably have been delivered by cesarean section at 38 weeks. Two immature infants were lost as a result of the mismanagement of severe maternal rheumatic heart disease with failure. One case of uterine inertia was poorly managed during labor and delivery. One patient with intermittent fetal distress was observed for 2 hours before a sterile vaginal examination disclosed the cervix to be 4 cm. dilated and the cord prolapsed.

TABLE VII. ERRORS IN THE OBSTETRICAL MANAGEMENT OF CASES WITH PREMATURE RUPTURE OF MEMBRANES

ERRORS IN MANAGEMENT	INFANTS 400-2,000 GRAMS	INFANTS ABOVE 2,001 GRAMS
Improper management of abnormal presentations:		
Breech	1	1
Transverse lie	0	1
Improper treatment of maternal diabetes	1	2
Improper treatment of rheumatic heart disease	2	0
Improper management of uterine inertia	0	1
Improper management of prolapse of the umbilical cord	0	1
Failure to treat intrapartum infection with antibiotics and oxygen	4	4
Total	8	10
Total fetal and neonatal deaths with premature rupture of membranes	52	23

The Treatment of Infection

Twenty-four, or 32.0 per cent, of the mothers of the 75 infants who died after premature rupture of the membranes had antepartum or intrapartum infection. Fourteen of these 24 infants with infection were alive at the onset of labor and 8 of them were not treated with antibiotics and/or oxygen during labor.

Guilbeau and Eastman[7] have presented conclusive data that the administration of penicillin during the latent period has no effect on perinatal mortality. It appears that the use of the wide-spectrum antibiotics would also be ineffective during the whole latent period; they may be contraindicated since the balance of the bacterial flora would be affected.

The use of wide-spectrum antibiotics, however, becomes mandatory after the onset of infection during the latent period and during labor and the puerperium. It also seems reasonable to administer 40 per cent oxygen to mothers who have an elevation in temperature of 100° F. or more during labor. An elevation in temperature increases the metabolic need of the infant for oxygen and its administration to the mother will increase the partial pressure of the circulating oxygen and improve its passage across the placenta.

The parenteral administration of tetracycline or chloramphenicol and the use of oxygen may not have prevented these 8 deaths. It is felt, however, that there are good theoretical grounds for the use of both agents and that they should have been used.

Socioeconomic Factors

Previous review of the material in the North Carolina perinatal mortality study revealed that socioeconomic factors were probably of major importance in the causation of fetal and neonatal deaths. Since premature rupture of the membranes is so intimately associated with the problems of prematurity and obstetrical complications, an analysis of the data was made for parental and environmental factors.

Table VIII is a study of the percentage distribution of cases of infants weighing from 400 to 2,000 grams according to race, father's occupation, and mother's education. It was impossible to compute death rates according to these factors since there were insufficient controls in this weight group. Death rates would have had little meaning since prematurity is of major importance in this class of infants.

TABLE VIII. SOCIOECONOMIC FACTORS IN FETAL-NEONATAL DEATHS OF 400-2,000 GRAM INFANTS WITH AND WITHOUT PREMATURE RUPTURE OF THE MEMBRANES ACCORDING TO PERCENTAGE DISTRIBUTION OF CASES

	NO PREMATURE RUPTURE OF MEMBRANES	PREMATURE RUPTURE OF MEMBRANES
Race.—		
Total	100.0	100.0
White	67.3	50.9
Non-white	32.7	49.1
Father's Occupation.—		
Total	100.0	100.0
Group I	21.1	19.1
Group II	37.9	31.9
Group III	41.1	48.9
Mother's Education.—		
Total	100.0	100.0
13 or more years	23.6	13.8
9-12 years	55.6	44.8
8 years or less	20.8	41.4

Premature rupture of the membranes in the smaller weight groups occurred more frequently in the non-white race. This is evident in the analysis for race and for mother's education because the majority of patients who had 0 to 8 years of schooling were non-white.

The father's occupation was classified in three groups. Group I consists of professional people, managers, officials, proprietors, and students in the Universities. Group II consists of clerks, sales workers, craftsmen, foremen, and operators. Group III includes farmers, farm laborers, other laborers, and household workers. It is clearly evident that the largest portions of the fetal and neonatal deaths of these small infants, with and without premature rupture of membranes, occurred in the lowest socioeconomic group. But the difference between occurrence and nonoccurrence of premature rupture of the membranes was so slight that it is difficult to say that the event itself is related to the father's occupation.

There were sufficient control infants weighing 2,000 grams and above to allow calculation of death rates for various socioeconomic factors in these cases.

TABLE IX. DEATH RATES PER HUNDRED DELIVERIES BY RACE OF ALL INFANTS ABOVE 2,001 GRAMS WITH AND WITHOUT PREMATURE RUPTURE OF THE MEMBRANES ACCORDING TO FATHER'S OCCUPATION

OCCUPATION GROUP	NO PREMATURE RUPTURE OF MEMBRANES	PREMATURE RUPTURE OF MEMBRANES
White.—		
I	1.17	1.08
II	1.99	0.76
III	1.61	6.17
Non-white.—		
I	--	--
II	1.02	2.13
III	2.84	11.29

Table IX presents interesting data concerning the relationship of the father's occupation to premature rupture of the membranes. When this complication occurs with infants over 2,000 grams of mothers in the upper economic

groups it is of minor importance. But when premature rupture of the membranes occurs in the lower economic groups, both white and non-white, it is a particularly lethal complication. This is undoubtedly related to the major obstetrical complications that accompany premature rupture of the membranes in these groups.

Table X is concerned with death rates in the white and non-white patients according to the mother's age. It is evident that there should be an increase in the death rate in both the premature rupture group and the non-premature rupture group above 30 years of age. In the white population, this increase is of the same order of magnitude whether or not the membranes have ruptured prematurely. In the non-whites under 30 years of age, with infants over 2,000 grams, premature rupture of the membranes was not a serious complication. But the difference in death rates becomes striking in the non-white patients who are over 30 years of age and have premature rupture of membranes. It is in these cases, however, that we find the highest incidence of toxemia of pregnancy, premature separation of the placenta, intrapartum infection, and abnormal presentations.

TABLE X. DEATH RATES PER HUNDRED DELIVERIES BY RACE OF ALL INFANTS ABOVE 2,001 GRAMS WITH AND WITHOUT PREMATURE RUPTURE OF THE MEMBRANES ACCORDING TO MOTHER'S AGE

AGE	NO PREMATURE RUPTURE OF MEMBRANES	PREMATURE RUPTURE OF MEMBRANES
White.—		
Less than 20	1.83	1.08
20-30	1.27	1.08
Above 30	2.46	2.62
Non-white.—		
Less than 20	1.88	2.13
20-30	2.01	2.83
Above 30	3.75	17.86

The southern part of the United States is fraught with many obstetrical problems. There are a large number of mothers who live under extremely poor socioeconomic conditions. These people have poor dietary habits and nutrition.[9] Perhaps worse, formal education is lacking, and either they do not perceive the need of preventive medicine and prenatal care or they fail to use it when it is offered to them. In Table XI, the highest perinatal mortality rates both with and without premature rupture of the membranes occurred in the groups of mothers who had only elementary and grammar grade education. Whether or not better education is the solution to this problem is unknown because it may be a relationship of association only. It is a hypothesis worth pursuing, nevertheless.

TABLE XI. DEATH RATES PER HUNDRED DELIVERIES IN ALL INFANTS ABOVE 2,100 GRAMS WITH AND WITHOUT PREMATURE RUPTURE OF THE MEMBRANES ACCORDING TO YEARS OF MOTHER'S EDUCATION

YEARS OF EDUCATION	NO PREMATURE RUPTURE OF MEMBRANES	PREMATURE RUPTURE OF MEMBRANES
Total	1.66	2.13
13 or more	1.05	0.63
9-12	1.71	2.44
0-8	3.01	5.41

It is difficult to draw definite conclusions from these data. It is evident that premature rupture of the membranes occurs frequently among patients seen in medical centers of the type surveyed here. It is often associated with major obstetrical complications. It can within itself be a lethal complication especially for the infants of the older non-white mothers and is more prevalent in the lower socioeconomic groups. It adds great gravity to the major obstetrical complications that befall these mothers and often is the final blow that brings death to their infants.

Summary

A sample of cases of spontaneous premature rupture of the membranes associated with the delivery of approximately 7,500 infants weighing 400 grams and above is presented.

The over-all incidence of premature rupture of the membranes was 15.8 per cent. The incidence of premature rupture of the membranes among the fetal and neonatal deaths was 26.7 per cent.

Premature rupture of the membranes occurred in association with a sizable number of major obstetrical complications. Infection was the principal lethal factor in the infant deaths which were primarily due to premature rupture. It occurred more frequently among the non-white and less educated mothers, and was tolerated less well by the older mothers from lower socioeconomic groups, whether the classification was based upon the mother's education, race, or the father's occupation.

Premature rupture of the membranes is a major obstetrical complication which requires additional study.

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Discussion

DR. HERBERT M. BLACK, Columbia, S. C.—In Table IV, the authors show that apparently 50 per cent of the infants were possibly lost because of this complication. They feel that a latent period greater than 48 hours in cases of mature infants increases the mortality three times. There seems to be no such correlation in infants below 2,500 grams. It is of considerable interest that all the full-term infants who died of infection had latent periods greater than 36 hours. We might consider this the "critical hour."

Errors in the obstetrical management of patients with premature rupture of the membranes (Table VII) occurred in 25 per cent of all cases. It seems that this is a little high in three teaching institutions, if I interpret this correctly.

The management of these patients should be along the following lines: (1) hospitalization; (2) sterile vaginal examination for correct diagnosis of ruptured membranes, presentation, abnormalities, etc.; (3) sulfonamides (if the patient is not sensitive) until 48 hours following delivery; (4) instruction in the proper hygiene to prevent infection; (5) awaiting the spontaneous onset of labor if premature, medical induction, if at term; (6) discharge of the patient if the onset of labor does not occur within 72 hours, with a daily report of temperature and fetal movement; (7) cesarean section only when other indications make this necessary.

Abnormal conditions associated with early rupture of the membranes should be prevented in the preconception period. It is our responsibility to emphasize good general health, normal endocrine relationships, and normal secretory endometrium before conception, rather than to search for something to do after the accident has occurred.

DR. A. R. GARNETT, Norfolk, Va.—In the belief that there is general indifference to this problem and that the caliber of obstetrics practiced in the Norfolk, Virginia, area is fairly representative of that practiced in areas with similar facilities, a check was made in the record rooms of the three local hospitals. The result was quite revealing. In the first, which has a three-year, Board-recognized training program, in the year 1955 the recorded incidence of premature membrane rupture was found to be 0.99 per cent in 2,458 deliveries; in 1956, 0.7 per cent in 2,614 deliveries. In the second hospital, which also has a Broad-recognized training program, the head of the record room informed us that no record was kept of these cases; the nomenclature, premature rupture of the membranes, was not used. And in the third, a private hospital with no clinic patients, a similar situation was encountered. Another point of interest, in the first hospital mentioned, approximately 20 physicians do 99 per cent of the work in the Obstetrical Department and every case of recorded premature rupture came from the practice of 6 of these 20 physicians.

In the recent literature there is a definite paucity of material on this subject; however, what is available demonstrates incidence rates comparable to those reported by Dr. Flowers' group. The lack of general interest combined with a relatively high incidence indicates a lack of recognition that the careful handling of these cases constitutes one means of improving fetal mortality rates.

A simple regime might include the following listed in order of their importance: (1) diagnosis, (2) bed rest, (3) medications to decrease uterine irritability, (4) antibiotics, (5) induction, and (6) Cesarean section. To enlarge briefly on each:

Diagnosis is usually quite obvious. When questionable, visualization of the cervix and vaginal vault, Nitrazine or litmus paper to determine vaginal alkalinity, and, when these fail, Papanicolaou smears are quite helpful.

Bed rest is considered imperative, both to delay the onset of uterine irritability and, by relatively immobilizing the infant, to decrease the changes in positive and negative pressures which can take place after rupture of the membranes, and, hence, to delay intrauterine infection.

Medications to decrease uterine irritability can become an extremely controversial subject. When it is felt, however, that delay in delivery will move the involved fetus from a nonviable into a viable category, it behooves us to consider the merits of the several drugs available. The only note of caution here is sounded by Eichner and Kunin of Cleveland, Ohio, who feel that the combination of opiate derivatives and large doses of progesterone decreases the latent period between rupture of the membranes and delivery and hence should be avoided.

The use of antibiotics in an effort to decrease the incidence of morbidity in the mother and/or pneumonitis in the infant until delivery takes place, and, finally, the judicious choice of medical induction or cesarean section, depending upon the problem with which we are confronted, such as malpresentations, disproportion, or prolapsed cord, will result in obtaining viable infants with a good chance of survival.

By adhering to one of the many variations of this program, it is believed that a significant number of infants may be salvaged from a group the indifferent handling of which is

now exemplified by the case of the girl who, between the fifth month and term, calls her physician, informing him that she is leaking water, and is told to take it easy until she starts having cramps and then to call back.

DR. B. G. GREENBERG, Chapel Hill, N. C..—I would like to comment a little about some of the methodological problems that are involved in a study of this kind. First of all, as Dr. Flowers indicated briefly, this type of study is what we call a retrospective study; that is, we are sort of looking back over our shoulders at what happened after it happened. As such, a study of this kind is not designed to prove any causal relationships, for example, as to what causes premature rupture of the membranes or how to treat it. All we can hope to do in a study of this kind is to show very high associations between certain variables and use this information to suggest certain worthwhile leads, worthwhile in the sense of further investigation.

The data upon which these results have been obtained are rather preliminary. They were collected during the first 2 years of the study. Since that time we have collected 2 years of additional data, and we have also extended the study to two additional hospitals in the city of Charlotte.

We do not know actually when the membranes rupture in every case. Furthermore, we do not know when the onset of labor actually occurred. As it is, it is usually an arbitrary definition in terms of cervical effacement.

The point which we would like to consider here is the methodological point that Dr. Garnett mentioned with regard to his investigation of this condition in his own city. He found premature rupture of the membranes in less than 1 per cent of the cases. My guess is that the obstetricians recorded premature rupture of the membranes only when it resulted in an overlong latent period.

Consequently, it is very important in a study of this kind that we give consideration to the methodology. Here, in choosing a comparison group, it is important that we use the same consideration as to who goes into this study, and that we have no influence in choosing who goes into the comparison group. The comparison group is chosen after the child is born so that none of the entries in the mother's file were influenced by previous knowledge that the child was going to be a comparison one. Such knowledge might influence the decision as to whether to write down "premature rupture of the membranes" or "non-premature rupture of the membranes."

We think that is important in any control study—that the control or comparison group be chosen at the same time, in the same place, in the same manner, and treated by the same personnel, and not consist simply of a historical review of cases of 5 or 10 years ago.

DR. FLOWERS (Closing).—Dr. Black has pointed out that we felt there was an error in management in approximately 25 per cent of the fetal and neonatal deaths with premature rupture of the membranes. We have attempted to make a critical study of our perinatal mortality; possibly we have been hypercritical, but we are attempting to improve our perinatal mortality.

Dr. Greenberg has commented that this study was not designed to determine the proper obstetrical management of patients with premature rupture of the membranes. But the management of this complication is of primary importance, and I am grateful for the timely remarks of our discussants.

A POSITIVE CYTOLOGY REGISTRY: SOME OBSERVATIONS ON THE EFFECT OF PREGNANCY MADE WITH ITS ASSISTANCE*†

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A POSITIVE Cytology Registry was established at the Jackson Memorial Hospital–University of Miami in 1956 and has steadily increased its scope and usefulness since then. This Positive Cytology Registry is an idea, an area in the hospital, an accumulation of office equipment and, above all, an assembly of people devoted to the aims of the Registry. These aims are service to the women who have or might have genital cancer and the collection of data that will be useful in finding the place of cytology in obstetrics-gynecology.

Organization

The Positive Cytology Registry was started and accomplished its first objective in July and August, 1956. This mission was to find as many as possible of the staff obstetric and gynecologic patients who had had positive cytology at the Jackson Memorial Hospital. One half of these patients were found and examined and the essential information on all the case histories collected in one file. This work was done by a medical student working under a United States Public Health Service Student Research Fellowship, a clerk lent to us by the Cancer Teaching Office of the Department of Pathology, and a member of the Department of Obstetrics-Gynecology, Dr. Harvey Lozman. All members of the secretarial staff in Obstetrics-Gynecology contributed some portion of their time to this first collection of data. The results of this effort have been reported by Ferguson and Lozman.[1]

In April, 1957, the National Cancer Institute began its support of the Positive Cytology Registry and this provided for two full-time workers, the purchase of office equipment, and other necessary expenses. With this expansion it was possible to intensify the search for patients lost to follow-up and to improve our capacity to keep in touch with all women matriculated into the Registry. At the same time important medical data on the patients could be gathered more efficiently. The work of the Positive Cytology Registry may sound very like the job of a Cancer Registry but at the time a cancer registry

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was not functioning. Furthermore, cancer registries do not seem to be prepared to assume responsibility for women who have positive cytology or questionable smears, without having proved cancer. A large portion of our interest lies in the women who have positive smears, but have not been proved to have cancer.

The core of the Positive Cytology Registry equipment consists of 4 files and a Registry Book. All cytology and tissue reports are kept on file under the patients' names. Each patient with positive cytology is represented in three files: a file for medical data, one for tracing information, and a file for recall dates.

The service component of the function of the Registry centers on health education. The registry worker explains in the patient's vernacular what "positive cytology" means. She is told what she will need to complete the diagnosis and, in time, what treatment is planned for her. As the patient begins to understand the necessity of periodic examinations we have generally found her grateful and cooperative. To date only 4 women have refused to come to the clinic or go to a private physician.

A great portion of the time of the registry workers is occupied with finding and talking to patients who do not appear for a scheduled return to the clinic. Many of the patients are difficult to find or have to be persuaded to return to the clinic. Intensive case-finding methods, as far as we know, have never been developed in the Miami-Southeast Florida region. Conditions peculiar to an area that includes migratory field workers and other itinerants, non-English-speaking Caribbean peoples as well as poorly educated Negro and white patients posed some problems entirely new.

The patient who fails to appear for a clinic appointment is first approached by letter directed to her latest known address. Many times the letter returns because the patient does not live at that address. Some patients can then be found with the assistance of the records at license bureaus, local police precincts, credit bureaus, the patient's church, her or her husband's place of employment, the power and light company, local stores, welfare agencies and charity organizations. Constant rechecking with the hospital social service department and the hospital admission desk occasionally uncovers a patient who has been lost to follow-up.

When these efforts fail to bring the patient to the clinic or to find her, a visit is made to her last address and other possible residences. In the first 6 months of the Registry's existence 130 home visits and field trips were made. If the woman is found she usually can be induced quickly to return to the clinic by a patient explanation of the importance of more tests. Thirty-nine women with repeated positive smears were brought to the hospital for diagnostic procedures; 19 of them had invasive or intraepithelial carcinoma.

If a woman has moved, the neighbors are questioned as to her whereabouts. A good deal of pertinent information can be turned up at this time. The visit to the patient's home in the effort to locate and talk to her has

proved an excellent opportunity to discuss not only the problems of the patient involved but also to interest the neighbors, friends, and relatives in the need for a yearly checkup and the importance of having a cervical smear. These women are impressed that anyone should exhibit such interest.

An important part of the service to the patient is the physical following of the reluctant woman through the Out-Patient Clinic. As a patient enters the clinic she is met at the reception desk, the reason for her visit is again explained to her and the importance of repeated examinations stressed. A Registry worker is on hand at all gynecology clinics. Many red-tape difficulties are easily handled at this time and the patient's visit is expedited in a way that encourages her return visits.

When a patient becomes a matriculate in the Positive Cytology Registry her permanent record cover is stamped in red ink with 2 inch letters "P.C.R." for Positive Cytology Registry. A doctor examining this patient at a future date in any department of the hospital will know that she had a positive cytology at some time. This inevitably leads to the taking of another smear and contributes to our history of this patient's exfoliation of cells. Meetings are held with various hospital groups such as social service, Out-Patient Clinic personnel, residents, interns, nursing instructors, and laboratory workers in order to familiarize them with the Registry, its aims, and the meaning of the letters "P.C.R." on the record cover. These meetings prove most helpful and result in an enthusiasm that makes everyone an auxiliary in the Registry.

Some patients, because of increased earnings, become ineligible for treatment in the clinic and are referred to a private physician. This physician is furnished with an abstract of the patient's history and all the information that we are capable of providing. We bring our histories up to date by periodic telephone calls to the physician's office. Patients who have moved out of the county or state have been traced and reports on the patient's condition have been obtained by requesting a simple form to be completed and returned. The importance of periodic cytology examinations, particularly in these patients, has been brought to the attention of many private physicians by the Registry through this activity. Fifty-three of our patients are being followed by private physicians.

Basic Data

By July 1, 1957, we had acquired a file of 350 patients with positive cytology. This represented the yield out of 16,000 studies done since cervical cytologic examination became a routine in the gynecologic outpatient department in March, 1952, plus a small number done in the preceding years; the same routine was established in the antepartum and postpartum clinics in November, 1955. Of these 350 women with positive cytology, 293, 84 per cent, had their follow-up brought up to date in 1957 by the Positive Cytology Registry.

All of our smears are made by a surface-cell scraping with a wooden spatula. Two slides are prepared at each examination.

"Positive cytology" as used in this report means a slide that contains cancer cells or cells that are suspiciously like cancer cells. The smears from our laboratories that are termed "positive" are the equivalent of Papanicolaou's Classes III, IV, and V.

A considerable number of these patients with positive cytology never had been proved to have cancer, invasive or intraepithelial. The opportunity to learn more about women who exfoliate these puzzling cells is one of the unique features of the Positive Cytology Registry.

We are reporting now only those aspects of our experience that have some relationship to pregnancy. The capacity of pregnancy to initiate or to accelerate the exfoliation of abnormal cells, if such an attribute exists, certainly needs assessment. We have observed a widespread sentiment that cytologic studies during pregnancy are near worthless, or, at least, too misleading. Coupled with this disregard of pregnant women is the attitude that women below a certain age, we have heard it said 30, do not need a routine cytologic examination. Thirty-two per cent of all our women with positive cytology are 29 years of age or younger. As so many women are available for pelvic examination only when pregnant, it would be regrettable to miss this cancer detection opportunity, if cytologic examination is of some value.

An association of cancer of the cervix and multiparity has been recognized for a long time. Of the 350 matriculates in the Positive Cytology Registry, 7 per cent had never been pregnant. As a comparison the records of 350 unselected women of 16 years and over who attend the Medical Out-Patient Department were used as controls; 16 per cent of them were nulligravidas. This low prevalence of nulligravidas in the group with positive cytology is statistically significant.

At the Jackson Memorial Hospital–University of Miami our experience has led us to the conclusions: that antepartum and postpartum clinics match other clinics in value as cancer detection and education centers; that abnormal smears obtained during pregnancy deserve the same attention as those obtained from nonpregnant women.

Some Basic Premises on Cytology in Pregnancy

I. If pregnancy itself causes an important degree of exfoliation of abnormal cells we might expect that there should be a sizable number of pregnant women with positive cytology and no serious cervical disease.

In our Registry there were only 21 women who were pregnant at the time when their first positive smear was obtained. As can be seen in Table I, most of these women had lesions that merited further study and treatment. Ten eventually needed hysterectomy. Eight of these pregnant women had intraepithelial carcinoma of the cervix and one, invasive carcinoma. In 2 cases the final diagnosis was basal-cell atypism. Four had only cervicitis. The fact that 6 women had no tissue diagnosis has various explanations and does not represent our plan of management.

TABLE I. TISSUE DIAGNOSES IN WOMEN PREGNANT AT TIME OF FIRST POSITIVE CYTOLOGY

Intraepithelial carcinoma	8
No tissue diagnosis	6
Cervicitis	4
Basal-cell atypism	2
Invasive carcinoma	1
Total	21

Eighteen of these 21 patients had never had a cytologic smear made before. The 3 who had had smears examined before pregnancy had negative smears (2, 8, and 18 months before). Without previous cytologic study one cannot be sure that the pregnancy induced the positive cytology. The importance of this is lost sight of in many estimations of the relationship between pregnancy and neoplastic tendencies.

A logical step is to compare these 21 pregnant women with patients not pregnant at the time of the first positive cytology and in the same age group (16 to 42 years) as the pregnant patients. There are 155 qualifying nonpregnant women but the disparity in the size of the two groups does not yet permit valid comparisons.

II. If pregnancy encourages exfoliation of abnormal cells we would expect the condition of nonpregnant women who had positive cytology to deteriorate when they subsequently become pregnant.

This did not seem to be true of our women. Utilizing only the 293 women whose follow-up was brought up to date in 1957, we learned that 29 of these patients have had 46 pregnancies since their first positive cytology. Two women had as many as four pregnancies subsequent to their first positive cytology and are now free of disease and have negative cytology.

Only one woman of the 29 had a worsening of her cytologic classification and 3 remained unchanged. Four women improved in the sense that their smears changed from positive to the simple exhibition of atypical cells, i.e., fitted into the negative cytology classification. Twenty-one women had exfoliated cells that became entirely normal. Stated otherwise, 25 of the 29 women lost their positive cytology over the follow-up period. This follow-up ranged from 10 months to 5 years and 9 months with a median of 3 years and 5 months. All 29 were living and well at their last 1957 follow-up.

What sort of treatment did these 25 women have whose smears became negative? Only 3 had hysterectomy or radiotherapy. Nine had no treatment or any of the diagnostic procedures which we feel must often dispose of the areas that are exfoliating the incriminatory cells. The remaining 13 had punch and cone biopsies.

The cervical tissue diagnoses in these cases are given in Table II. One woman had invasive carcinoma, 5 had intraepithelial carcinoma, and 2 cases were labeled basal-cell hyperplasia.

TABLE II. CERVICAL TISSUE DIAGNOSES IN WOMEN PREGNANT SINCE FIRST POSITIVE CYTOLOGY

No tissue diagnosis	12
Cervicitis	9
Intraepithelial carcinoma	5
Basal-cell hyperplasia	2
Invasive carcinoma	1
Total	29

III. If pregnancy is an important inciter of positive cytology, we might expect it to disappear after the pregnancy.

Here our figures are equivocal. Ten remained positive and eventually needed hysterectomy. Seven of the 21 women with their first positive cytology during pregnancy became negative after the pregnancy. Five of the 7 women who became negative had no treatment and no cone biopsies performed; 2 women had only punch biopsies. Four women had no further cytologic work done because they were lost to follow-up.

Thus it appears that positive cytology can disappear after pregnancy in some instances. In the 2 women who had punch biopsies it is conceivable that these procedures were responsible for the disappearance of the positive cells. Did the reversal from positive to negative cytology in the other women occur because the inciting factor of pregnancy was removed? With the accumulation of more cases in the next few years and the effective follow-up provided by the Registry we hope to be able to help answer this question.

In appraising the improvement in cytologic diagnosis that has been noted in the weeks and months after delivery, we must remember that the same improvement can be noted in nonpregnant women. In our Registry we have 78 cases of "spontaneous" disappearance of positive cytology. These women have had a reversal from a positive cytology to a negative one without the benefit of hysterectomy, radiotherapy, or excision of the cervical stump. These 78 women all have an interval of at least 6 months between the first positive cytology and their last negative one. These "spontaneous" disappearance cases range from a minimum of 6 months to 6 years and 8 months, with a median time of 2 years and 7 months. Another 15 women had this reversal to negative cytology and are not included yet in our figures because the follow-up is less than 6 months.

Thirty-two of the "spontaneous" disappearance cases had no treatment or diagnostic procedures that could have contributed to the favorable cytologic change. The remaining 46 women did have vigorous diagnostic or therapeutic attention to the cervix and until proved otherwise we will have to give credit to these measures as constituting successful treatments. These treatments were as follows: 28 of the treated women had a cold conization of the cervix; 9 had only punch biopsy; another 9 had various combinations of curettage, excision of polyps, punch biopsy, and cauterization.

The cervical tissue diagnoses in these women with "spontaneous" disappearance of the positive cytology are given in Table III. Cervicitis was the most common diagnosis. Six women had basal-cell hyperplasia and related diagnoses and only one intraepithelial carcinoma. There might have been many more women with these diagnoses of neoplasia if we had not done so many hysterectomies for these conditions, automatically disqualifying them for this "spontaneous" disappearance category. This assumption is based on the frequency with which we found no residual disease in the surgical specimen after hysterectomy. The original diseased areas of the cervix were removed by excisions of tissue for biopsy.

TABLE III. CERVICAL TISSUE DIAGNOSES IN 78 NONPREGNANT WOMEN WITH "SPONTANEOUS" DISAPPEARANCE OF POSITIVE CYTOLOGY

Cervicitis	38
No tissue examined	30
Basal-cell hyperplasia, etc.	6
Cervical polyp	3
Intraepithelial carcinoma	1
Total	78

Conclusions on Treatment of Positive Cytology in Pregnancy

Comment on our plan of management of women with positive cytology is in order because some of the information presented here might lead to misinterpretation as to how we handle such cases. Actually, many patients were not handled in our usual way for various reasons, including lack of patient cooperation, irregular residence in the area, and transfer to private physicians who had different ideas on management.

The Influence of Positive Cytology Registry Data.—We have not been able to find any data in our Positive Cytology Registry that discourage the continuation of departmental policies as they will be stated. Indeed, some of the

routines have evolved from an early appreciation of trends as they appeared during the gathering of these data. There is very little difference in our management of pregnant and nonpregnant women with positive cytology.

1. All women regardless of age or pregnancy should have a genital cytologic study done by the gynecologist or obstetrician when first seen. Support for this contention comes from the observation that of the 21 women pregnant at the time of the first positive cytology, 10 had a cervix of normal appearance and 16 had no bleeding. This test should be repeated at certain intervals, depending on the initial cytology and other histologic evidence.

2. Women who exfoliate abnormal cells should be followed by cytologic and other studies until completely negative smears are obtained. Some women, notably those with positive cytology, should be followed forever.

3. When a lesion is visible on the cervix it should be excised for biopsy, whether the patient is pregnant or not. The reasons for these precautions are the very few, but very disturbing, false negatives obtained in the presence of a visible cancer.

4. If a woman is pregnant the safest course is to assume that the pregnancy is not responsible for the positive cytology. With proper respect for the pregnancy, studies should be completed very much the same as in the nonpregnant. We have had but few complications from punch or cone biopsies in pregnancy. No pregnancies have been lost.

5. Punch biopsy alone is not sufficient study in the following circumstances: (a) intraepithelial carcinoma of the cervix; (b) persistence of positive cytology and a tissue diagnosis of cervicitis, basal-cell atypism, or any report less than frank malignancy; (c) prolonged exfoliation of any grade of atypical cells.

Reference

1. Ferguson, James Henry, and Lozman, Harvey: South. M. J. 51: 296, 1958.

Discussion

DR. J. ERNEST AYRE, Miami, Fla.—A positive cytology registry indeed performs an important and much-needed function in a department of gynecology and obstetrics or any cytology laboratory or center undertaking cervical cytodiagnosis. The great sensitivity of the cytologic method in detecting preclinical cancer or precancerous cell changes provides the gynecologist with a valuable new method of observing tissue growth and cell behavior, which represents not only a method of early cancer diagnosis but actually of achieving an important measure of cancer prevention, through precise diagnosis of cells of the precancer cell complex type (or dyskariosis as some cytologists prefer to call these cells). The efficiency of cauterization or electroconization or "ring biopsy" in destroying or eliminating such premalignant cells can be accurately determined by follow-up cell smears or scrapings.

At the Miami Cancer Institute where special teams of cytologists and cytotechnologists engage in cytology screening and diagnosis, over 90 per cent of the specimens submitted by more than 1,300 participating physicians, city health clinics, and nine smaller hospitals represent gynecologic cell tests. The educational program designed to promote routine cervical cytology on all women over 20 has been so successful that after 7 years the volume has increased to exceed 1,000 tests per week. A Remington Rand tabulating machine is used for statistical recording and continuous and vigorous efforts are necessary to make the follow-up

program effective. Departments of gynecology such as Dr. Ferguson's have certain advantages in the follow-up of patients handled by them directly while the cytology center deals not with patients but with the practicing physicians and specialists. We do follow special groups of research patients ourselves for cytochemical, cell behavior, and other basic research studies, including tissue-culture manifestations. But the Institute does not deal with diagnosis in the patient, endorsing the principle and applying to good advantage the dictum that the physician's office is the best cancer detection center.

I would like to say a few words concerning the effect of pregnancy on positive or abnormal cell findings. In a recent report given by Dr. Wayne Rogers, Crane, Castillo, and others from the Miami Institute, studies on 2,000 pregnant women show no increase in anaplasia (that is, positive or suspicious lesions) as compared to a similar group of nonpregnant patients of comparable ages on whom the studies were done routinely.

It was observed that most normal pregnancies show entirely normal cells. We have been making a study of this very interesting problem for more than a decade and see an excellent opportunity for useful research pertaining to cancerogenesis. We have observed that whenever the cervix is involved in extreme inflammatory hyperplasia there is a considerable aggravation of cytologic abnormalities. But we do not subscribe to the concept that pregnancy per se will induce pseudomalignant cellular and tissue changes. It seems more likely that cytology applied during pregnancy will draw attention to latent neoplastic activity likely to become clinically evident in future years. The following points should be borne in mind: pregnancy increases the amount of mucus continuously secreted from the cervix; the normal rhythmic ebb and flow of the sex cycle are absent. We found evidence using paper chromatography that estrogen is present in the cervical mucus and this is reflected in abnormally high cornification when precancerous or cancer in situ cell changes are present. During pregnancy this situation is remarkable because normal pregnant women usually show a total absence of cornification. It is quite probable, too, that estrogen becomes concentrated in the chronically inflamed tissues surrounding in situ and related lesions, accounting for the high cornification in cell scrapings. Wishful thinking has led some to believe that the pregnancy secretory hormones in some way cause regression of in situ lesions. We have not found all the answers to the many provocative questions which arise in this stimulating study but the opportunity for profitable research is evident.

In our experience when biopsies and cauterization are withheld, regression of true carcinoma in situ lesions during or following pregnancy is rare. In fact, we have never seen it except where biopsy or cautery has been brought into play. After biopsy one cannot say "spontaneous" regression if the lesion is not reconfirmed in the second biopsy. Most careful postpartum cell scrapings will sometimes yield tiny nests of involuted cells which are still active and will frequently achieve accelerated growth at some future time, and progression ultimately to invasive cancer is believed to be the most common fate of such cells and lesions.

We believe that in situ or precancerous lesions will undergo both hypertrophy during and involution following pregnancy. Therefore if the study method is based upon biopsy the nests of cells will be more difficult to find after pregnancy. Then, too, the dangers of repeated biopsy in extirpating discrete embryonic malignant lesions are evident.

Carcinoma in situ lesions and the related premalignant stage lend themselves most effectively to repeated gynecologic follow-up with cytology. Gynecologic cytology is a precise, highly accurate diagnostic procedure. This aspect alone speaks strongly in favor of a positive cytology registry such as Drs. Ferguson and Cavanagh have described.

It is good to see that Dr. Ferguson recommends ring biopsy more or less routinely to confirm positive cytology. Formerly when the ring biopsy was first described in 1948 (Ayre, J. E.: J. A. M. A. 138: 11, 1948), this procedure necessitated hospitalization. Recently, however, since Dr. Carey Hiett of Fort Worth, Texas, and later Dr. Joseph Scott of Miami have popularized the method of infiltrating the cervical tissues with dilute Novocain to which a few drops of Adrenalin were added, it has become possible to perform a ring biopsy without any untoward bleeding whatsoever. Indeed, it has become so minimal that quite frequently the ring biopsy can be considered as suitable for use as an office procedure.

DR. JOHN C. ULLERY, Columbus, Ohio.—For the past year and a half we have had a method of screening all women over 20 in the city of Columbus, in Franklin County, and we have used aspiration only, as that is what the project was set to.

During that year and a half we have examined 76,000 aspiration specimens taken from the vaginal vault. We have discovered 196 gynecologic cancers in these patients. The 76,000 examinations represent 54,000 patients. The discrepancy in the figures, of course, is caused by the repeat examinations and the first-year recall that we have had. So we have found 196 carcinomas in situ and invasive carcinomas in 54,000 patients.

One of the interesting things that has come out of this report so far is the difference in the staging of the carcinomas that we have found in this group compared with studies that we made in our own gynecologic tumor clinic of previous years. According to our tumor clinic statistics in 1947 there were no Stage 0 carcinomas at all; 14 per cent were Stage I; 41 per cent were Stage II; 41 per cent were Stage III; 4 per cent were Stage IV.

In this cancer survey cytology group, 1957, 38 per cent were carcinoma in situ; 48 per cent were Stage I; 5 per cent were Stage II; 7 per cent Stage III, and 2 per cent Stage IV.

This, to us, has a terrific impact in that we are now making our diagnoses earlier. This has been very valuable. We have alerted the physicians in Columbus. The women of Columbus are coming down for annual pelvic examinations.

Early diagnosis is a very important phase of this cytology study. I think early and adequate treatment must go along with that, too. We have found some very interesting things as far as early and adequate treatment is concerned in these patients, but I am not prepared to speak of this now. We will learn that early and adequate treatment will probably in the end mean as much as early diagnosis—at least, it will closely parallel it.

As far as pregnancy is concerned, we have included all our obstetric prenatal clinic in our studies. We have taken aspiration specimens fr these patients prenatally, once every trimester, and we have found 3 carcinomas in this group. We have found 2 invasive cancers and one in situ. I believe our incidence of in situ carcinoma is less than you have in your cytology clinic down here.

By developing a program of taking aspiration specimens from these patients—it is a very simple and easy thing to do—we believe we are offering them the best opportunity for survival. The 2 invasive carcinomas that we picked up were both Stage I.

I am interested in one thing, and I would like to ask this of Dr. Ferguson. In the group of patients whose positive cytology had been found to be reversed—I believe, he said 32 had no treatment or diagnostic procedures—I am interested to know what role he thinks infection played in these patients and just what type of infection do these patients have. Was it Trichomonas, Monilia, or was it a bacterial infection? I would like to ask if he had any positive studies on these patients.

DR. WILLIS E. BROWN, Little Rock, Ark.—I should like to urge all of us and the pathologists and cytologists in particular not to believe too strongly in themselves. When we say that this desquamated cell is or is not a cancer cell, we are endeavoring to interpret the intent of this cell. We are endeavoring to say what this cell is going to do; not what it has done, but what it is intending to do—to invade, to metastasize, and to destroy.

Is it surprising, then, that we find in most series of cases so-called reversals, so-called changes, so-called spontaneous cures? I wonder if it has not been that we have believed too much in ourselves and have read an intent for this cell or this tissue beyond what is revealed.

I regret that in my own community, and I trust that it is not true here, we find efforts to recommend therapy based upon such interpretations of very equivocal material; as long as we see a modest percentage of reversals, then obviously we are misreading the intent of cell or tissue.

Let us realize that there are areas that are not clear, and since we as clinicians use the phrase, "Diagnosis deferred," we should grant the pathologist the same privilege of a deferred diagnosis. In this way we can remove a serious source of error and help remedy this inferiority complex of our colleagues.

DR. FERGUSON (Closing).—I am not sure that we are prepared to do cone biopsies as an office procedure. However, we should keep our minds open and possibly it can be done.

We do have a large experience with cone biopsy and are in a position to find out if it can be done as an office procedure, which I rather doubt. In the calendar year 1956 we had 132 done in the Jackson Memorial Hospital and in 1957 it has been estimated that we have had over 200 cone biopsies. We take a generous specimen for biopsy, reaching at least 1.5 cm. up into the cervical canal and include all of the lesion that can be seen on the portio.

The addition of infiltration of the cervix with an epinephrine-saline solution, which Dr. Ayre mentioned, is a real improvement. Those of you who were here in November for the meeting of the Southern Medical Association may recall the television program from my department in which Dr. Handte did a conization after infiltration of the cervix with that solution. There was practically no bleeding at all, nothing had to be touched with the cautery and no sutures had to be placed. The conization on the next patient was then done by Dr. Crews, without the infiltration of the hemostatic solution, and the comparison was so vivid that many in the audience became apprehensive.

Dr. Ullery has asked about the 32 patients in whom there was a spontaneous disappearance of the positive cytology. In my paper I have "spontaneous" disappearance surrounded by quotation marks because possibly these women will some day have a recurrence of this positive cytology. It may be that these women are more likely to have cancer of the cervix at some future date, or in some other part of the body, than will some control group.

The question of the importance of local infection has been raised. At present our data have not been analyzed for that factor. I suspect that vaginitis may have been responsible for some of the cases of minor grades of positive cytology which disappeared "spontaneously."

EXPERIMENTAL ENDOMETRIOSIS IN THE HUMAN*

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(From the Grady Memorial Hospital)

SAMPSON'S[1] theory of the histogenesis of endometriosis, although not the first, was the primary one of wide acceptance. Russell,[2] in 1899, having found endometrial glands in the ovary, suggested a theory of growth from cell rests of the Müllerian duct. Sampson, in 1921, surmised that the actual implantation of fragments of the shed endometrium that had been regurgitated from the fimbriated ends of the tubes explained the origin of the phenomenon. This seemd logical because "retrograde" menstruation can be observed at the time of laparotomy and the sites of implantation most frequently seen are in the cul-de-sac of Douglas or on the ovary closely adjacent to the tubal fimbria. Then these fragments would be expected to gravitate to these new sites of growth.

This theory was challenged, however, because of the rather frequent occurrence of endometriosis at sites where direct implantation would be impossible, viz., the umbilicus, inguinal lymph nodes, etc.; thus the theory of celomic metaplasia described by Iwanoff and Meyer, and championed by Emil Novak[3] gained popularity. Furthermore, Halban[4] demonstrated the "benign metastasis" of endometrial fragments through the lymphatics, as into the inguinal nodes.

Sampson,[8] thus challenged, eloquently stated, "If bits of Müllerian mucosa carried by the menstrual blood escaping into the peritoneal cavity are always dead, the implantation theory, as presented by me, also is dead and should be buried and forgotten. If some of these bits are even occasionally alive, the implantation theory also is alive." Therefore, the fundamental weakness in the Sampson theory, admittedly, was the inability to demonstrate that menstrually shed fragments are viable.

As the incidence of endometriosis has so amazingly increased, so has the interest in the enigma of its origin and behavior increased. There now seems to be a spirit of compromise between the protagonists of the various theories on the understanding that no one theory could explain all cases.

The viability of the shed endometrium of the human has never been proved in vivo although tissue cultures by Keettel and Stein[5] in 1951 showed that both epithelial and stromal elements could be grown artificially for a short period in the laboratory. Cron and Gey[6] had done previous pilot work and in 1927 reported growth by tissue culture but the results were mitigated by the fact that the uterine cavity had been invaded by "a small curette" in procuring the specimen. Te Linde and Scott[7] in 1950 reported their experiment on the rhesus

*Presented at the Twentieth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hollywood, Florida, Feb. 1 to 5, 1958.

monkey, in which the menstrual flow was shunted into the abdominal cavity or abdominal wall. Endometriosis developed. A few skeptics voiced doubt, however, because of the chance that the site might have been contaminated by cells spilled during operation, or even that metaplasia of the celomic membrane might have developed from the influence of the foreign-body reaction. Therefore, the problem presented itself of trying to prove or disprove that the cells of the shed endometrium could survive implantation in the human.

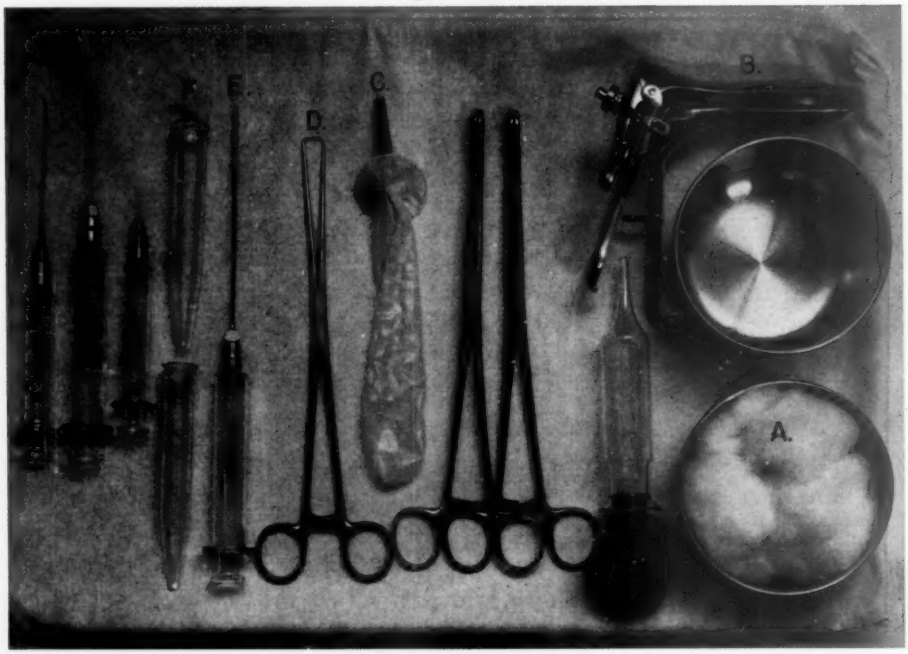

Fig. 1.—Apparatus as autoclaved for collecting and implanting specimen. *A*, Basins, syringe, and sponge forceps for preparation of vagina and vulva. *B*, Bivalve speculum. *C*, Colvin cannula and sac for collecting specimen. *D*, Tenaculum. *E*, Long needle and syringe for aspirating specimen. *F*, Centrifuge tubes. *G*, Syringes for local anesthetic infiltration and implantation of specimen.

Material

Selection of cases for this experiment was made from women, white and Negro, of the charity service of the Grady Memorial Hospital of Atlanta, Georgia. In an effort to give credible value to the experiment, it was to be projected to 25 cases. In the event that the results were all negative in this well-controlled experiment, it might cast even more doubt on the theory that shed endometrium was viable; in the event the results were positive, it would be proof that this shed endometrium was viable and could grow at sites of implantation in the human. All of the patients selected were to have been scheduled for laparotomy for other indications, such as myomas of the uterus. It was determined that the primary operation could be safely postponed for the given length of time necessary for growth of the shed endometrial fragments. No patients were chosen who had any suspicious menstrual irregularities or evidence of active pelvic inflammatory disease.

Of the great volume of patients seen in the clinic, 53 were found who seemed to qualify as acceptable. Of these, 32 either failed to cooperate or refused to

participate. Twenty-one cooperated and were admitted for study. Of this final group, 8 thus far have been studied while the remaining 13 were found unsatisfactory because of scanty flow, failure of the collecting device, or an obvious break in asepsis.

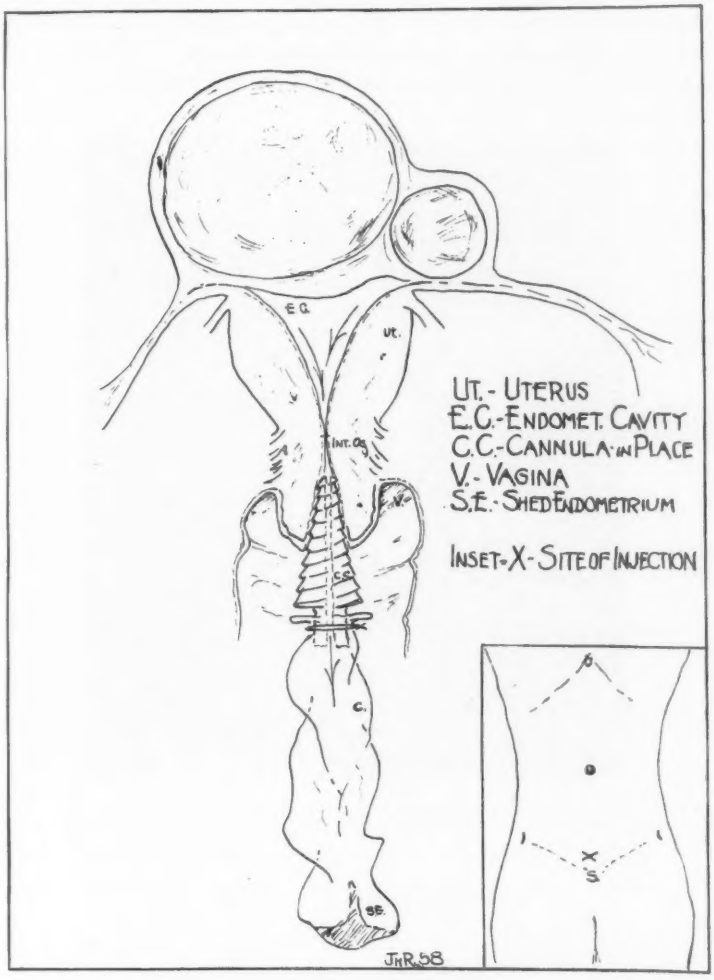

Fig. 2.—Collecting device in place. Tip of short broad cannula remains inferior to internal os. *Inset,* Site of implantation denoted by *X.*

Prior to the injection in the first case, extensive study was made, cytologically and bacteriologically, of the menstrual fluid collected according to the technique to be used in this experiment. Cultures made of the material were negative in both aerobic and anaerobic environment for pathogenic and nonpathogenic organisms that might have been present in the patient or contaminants. Cytologic studies were made of the sediment and supernatant portions of the centrifuged specimen by wet smear and Papanicolaou techniques. Fragments of tissue were found in the sediment.

Criteria

The criteria to be satisfied if this experiment was to be of value were necessarily critical. These were set forth: (1) The experiment must be harmless to

the patient. (2) The endometrial fragments were to be "shed." (3) The endometrial cavity could not be invaded for collection of the specimen. (4) The specimen must be collected by natural flow by gravity and without trauma. (5) The site of implantation must be extracelomic, extragenital, and at a site where no other operation had been performed. (6) The site of implantation must be apart from the expected drainage routes of the pelvic lymphatics. (7) The period for growth was to be 90 days or more. (8) Microscopic evidence of both glandular and stromal elements must be demonstrable.

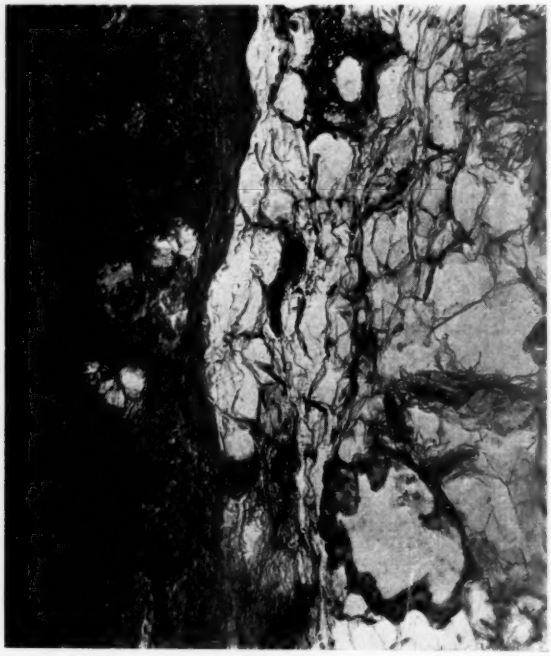

Fig. 3.—Low-power photomicrograph showing acini and scarring in Case 1. This is not interpreted as endometriosis but might suggest early evidence of growth (110 days).

Method and Procedure

A simple setup and procedure were devised (Fig. 1).

The patient was asked to report to the hospital at any time at the very onset of the menstrual flow. Under aseptic precautions, the short Colvin cannula with the condom attached was placed securely within the endocervical canal (Fig. 2) and the patient was put to bed, preferably in Fowler's position. After an elapsed time of approximately 12 hours when sufficient material had collected, the condom was clamped at its attachment and the device removed. The specimen was aspirated, placed in a sterile centrifuge tube and spun at high speed for 10 minutes. The sediment was drawn off preparatory to injection at the preselected site.

The site of injection for implantation was selected one fingerbreadth above the symphysis pubis in the midline where no previous operation had been performed and where the future incision was to be (Fig. 2, inset). The actual injection was made under local anesthesia and down onto the abdominal fascia. A No. 18 gauge needle was used. After the third case, penicillin-dihydrostreptomycin solution was given prophylactically intramuscularly in the buttock. The third patient had developed local cellulitis from what was thought to be

faulty surgical technique of injection. No other morbidity has been encountered. The patient was observed on the ward for 12 to 18 hours after injection and then allowed to go home. The patients were scheduled to return for the proposed laparotomy from 90 to 180 days after implantation was done. Upon re-entering the hospital, the patient was questioned about any local reaction, such as periodic pain; none was reported. At the time of the abdominal incision, the adipose tissue down the fascia at the site of implantation was removed en bloc and sent immediately to the pathology laboratory before the abdominal cavity was opened. The remainder of the operation was carried out routinely as indicated.

Results

Thus far 8 cases have been studied by injection and laparotomy (Table I); Case 3, however, was unsatisfactory for this study. Case 7 (see case report) showed gross and microscopic evidence of endometriosis at the site of implantation. Case 1 showed a definite nodule of scarring, with gland acini surrounded by an apparent stroma and lined with a cuboidal type of epithelium (Fig. 3). It is believed that this might possibly be an endometrioma showing some morphologic changes due to surrounding scar reaction. Case 6 showed scarring and peculiar cells thought likely to be those of reaction to foreign body.

TABLE I

PATIENT AND HOSPITAL NO.	AGE	RACE	DAYS ELAPSED AFTER IMPLANTATION	INCIDENTAL PATHOLOGY	RESULTS
1. E. E. G. 200964	37	Negro	110	Myomas of the uterus	Nodule of scarring and gland acini developed at site of implantation. The epithelium was cuboidal and the stroma questionable
2. Q. D. 383598	34	Negro	117	Myomas of the uterus	Negative
3. W. K. 380538	40	Negro	—	Myomas of the uterus	Unsatisfactory. Local cellulitis at site of implantation
4. A. H. 248301	38	Negro	179	Myomas of the uterus	Negative
5. N. S. 176154	38	Negro	150	Myomas of the uterus	Negative
6. M. H. 373760	40	Negro	183	Myomas of the uterus	Nodule of scarring with foreign body reaction at site of implantation
7. M. T. A254000	25	White	175	Myomas of the uterus	Endometriosis developed at site of implantation
8. C. C. 249507	32	Negro	195	Myomas of the uterus	Negative

Case report: Case 7, M. T., was a white, married nulligravida, age 25. Her chief complaint was pelvic discomfort due to a large uterine myoma (16 cm.). Implantation was done on March 1, 1957, and laparotomy performed Aug. 22, 1957, or 175 days after implantation.

It may be seen that both epithelial and stromal elements were present and encased to a moderate degree in scar tissue (Figs. 4, 5, and 6).

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4.—Case 7. Low-power photomicrograph of endometrioma.
Fig. 5.—Case 7. Greater magnification showing more of gland detail.
Fig. 6.—Case 7. High-power photomicrograph showing typical endometrial stroma and gland epithelium. Note scarring and exudate.

Summary and Conclusion

An experiment has been successfully carried out, proving that shed endometrium is viable and may be grown in vivo in the human. A brief review of the theories of the histogenesis of endometriosis has been given. The keystone of Sampson's theory as applied to the human has been established.

In adding this additional facet to our knowledge of endometriosis, it is hoped that further experimentation may be stimulated not only with regard to the histogenesis of the condition but with regard to its prophylaxis and treatment.

The criteria set forth for this experiment have been satisfied.

It is submitted that this is evidence that Sampson's theory is an acceptable explanation for the histogenesis of endometriosis, that the shed endometrium is viable and may be implanted within the host.

Appreciation is expressed to Dr. Tom D. Raaen, Chief Pathologist of the Grady Memorial Hospital, and his staff for their cooperation and work in preparing and reviewing the microscopic slides used in this experiment.

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Discussion

DR. BAYARD CARTER, Durham, N. C.—In viewing this material, we were impressed by the pathology slides and considered them to be slides of true endometriosis.

Previous experimenters, in their attempts to grow endometrium in the eyes of experimental animals, were unable to get growth of the implants when the endometrium which was implanted had been shed from the uterus.

The method used by Dr. Ridley and Dr. Edwards meets the necessary criteria for shed endometrium.

Have the essayists tried in these experiments to inject noncentrifuged menstrual discharge? Centrifuging of the menstrual flow theorectically gives a higher concentration of endometrial elements. We will hope that in the injection techniques used on some of the 8 patients they have in reserve, they will use it without centrifuging it.

This technique would add strength to the premise that endometriosis may be produced with shed endometrium.

DR. JAMES M. INGRAM, Tampa, Fla.—In comparing this human experiment with the classic animal experiments of Te Linde and Scott, one is impressed by the difference in the percentage of successful transplants. From 10 operations in monkeys, 5 implants of endometriosis were produced. Out of 7 attempts in the human, one transplant succeeded. It would be a logical assumption that the indirect method necessarily used in the human accounted for the difference.

The indirect method used here involves four factors, all of which are probably unfavorable to the viability of endometrium. They are: (1) the absence of nourishing medium in the centrifuged sediment, (2) temperature changes away from body temperature which occurred during the processing and injection, (3) the chemical action of the latex on the endometrial cells, and (4) the presumed longer time interval that the endometrium is in transit between uterine cavity and host site.

The first factor is perhaps the most intriguing. The function of the liquid secretion of the Fallopian tube and of the endometrium is to nourish the wandering ovum during its travel and early implantation. These secretions are rich in glycogen, protein, and electrolytes for this sole purpose. They might, also, serve the same purpose in nourishing the endometrium while it is in transit. In these experiments, a sediment rich in cells but low in fluid was used for injection. One cannot help but wonder if a higher percentage of transplants would succeed if more of the fluid were injected with the cells at the host site.

The factor of temperature maintenance was not mentioned by Dr. Ridley, but it is presumed that efforts were made to control it. The chemical and time factors would be difficult, if not impossible, to evaluate or to improve.

Although Sampson's theory does not explain all endometriosis, it explains the vast majority of cases. It should have and has received the greatest effort at experimental proof. Sampson wrote about his theory from 1921 until his death in 1946. His strongest opponent was Meyer. In his Munich *Handbuch* of 1930, Meyer stated that, if the viability of shed endometrium could be proved, the first question concerning Sampson's theory would be answered. The second question was soon raised as to whether the endometrial cell clumps could flow backward through the small lumen of the interstitial portions of the tube.

In 1933, Geist answered the second question by drawing menstrual discharge containing viable clumps of endometrium through a pipette, which was one third the diameter of the narrowest portion of the tube. In 1950, Te Linde and Scott proved that shed endometrium could be transplanted in monkeys. The first human transplant of shed endometrium is now reported by Drs. Ridley and Edwards. When this is repeated in subsequent human subjects, the two major questions of Sampson's theory will have been answered. Once proved, a theory becomes a fact. The term "Sampson's theory of the histogenesis of endometriosis" might well then be shortened to simply "Sampson's histogenesis of endometriosis."

DR. J. P. PRATT, Detroit, Mich.—I noted in the authors' table that their one successful transplant was in a young woman, aged 25, and that most of the other patients were older women. I hope it will be possible to continue this experiment and to use younger women. I believe that what we see clinically tells us that most of these endometrial implants occur at an early age. It is true that we often find them for the first time in the thirties or the forties, but that is because the patient has come to us for some other reason, and there is a very good reason to believe that endometriosis has been there for a long time.

DR. RIDLEY (closing).—In answering Dr. Carter's comment I would like to say that we used only a 1.5 to 2.0 c.c. volume of the centrifuged specimens, this being the sediment portion. We did not use the full volume because of wanting to avoid too great a dead space and also pain at the site of injection. I appreciate his good suggestion.

The same thing might be said in answering Dr. Ingram's observation. It is true that using more volume might increase the probability of survival of the shed cells.

Dr. Pratt, I would likewise be interested in the observation of a positive case in the older woman. Age very likely plays an important part. In gathering this material, beggars could not be choosers, and we had to take women with the more harmless, more predictable, and most prevalent pathology, namely, those with uterine fibroids. Of course most of them were found in the Negro race between the ages of 30 and 40.

All of this does stimulate us a great deal to continue and see if we can make some observations as to not only the interrelationship of age and race, but any other factors that might present themselves, now that we know that this experiment is safe and successful.

TOPICAL ANDROGENIC HORMONES IN VULVAR KRAUROSIS-LEUKOPLAKIA SYNDROME*

Preliminary Report

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THE troublesome affliction of the vulva designated as the "kraurosis-leukoplakia syndrome" causes much distress and misery to the patient. It perplexes and frustrates the physician, but seldom does it inspire any comprehensive study of its etiology, pathology, and treatment. The division of responsibility between dermatologists and gynecologists, the prolonged course of the disease with its spontaneous remissions and exacerbations, the inherent tendency of the unsatisfactorily treated patient to wander from doctor to doctor, and the quick resort of some physicians to vulvectomy—all contribute to confusion. At present, there is no universally accepted concept of the disease as a histologic entity. There is no proved etiology and, obviously, no specific treatment. On the other hand, the clinical picture generally is so characteristic that there is seldom doubt as to diagnosis.

None the least of the stumbling blocks in the approach to the problem is the lack of a uniform terminology. The term "kraurosis" introduced by Breisky[1] in 1885, though meaning dry or brittle, has come to connote the shrinkage or contracture of the vulvar skin which may be associated with leukoplakia, lichen sclerosus, or simple senile atrophy. Darier[2] in 1928 described kraurosis as a sclerosing progressive atrophy of the mucocutaneous teguments of the vulva, leading gradually to stenosis of the vaginal orifice, disappearance of the labia minora, frenulum, and clitoris, and flattening of the labia majora. The mucosa of the parts involved was described as always smooth, shiny, and dry. Complication by leukoplakia was noted as being frequent. Taussig[3] felt leukoplakia to be the earlier hypertrophic phase and kraurosis the succeeding atrophic phase of a single process. Hunt[4] stated that both leukoplakia and kraurosis are merely manifestations of lichen sclerosus. Wallace and Whimster[5] offered the following classification:

1. Primary atrophy of the vulva (identical with Darier's kraurosis). This may or may not be complicated by leukoplakia.

*Presented at the Twentieth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hollywood, Florida, Feb. 1 to 5, 1958.

2. Leukoplakia. This can be associated with primary atrophy or lichen sclerosus. It may occur independently, even on the nonatrophic vulva, with no evidence that it is invariably followed by kraurosis.

3. Lichen sclerosus. This is often associated with similar lesions elsewhere on the body and is frequently complicated by leukoplakia.

4. Senile genital atrophy. Usually asymptomatic, it is without significance except for its confusion with kraurosis.

On the basis of a limited experience we find Wallace and Whimster's classification as workable as any, but do not feel qualified to accept or reject their concept of these as four separate processes. Our Department of Pathology, upon which we are dependent for our histologic interpretations, follows essentially the criteria of Wallace and Whimster.

It is generally agreed that most vulvar carcinomas develop on a background of kraurosis and/or leukoplakia. Conversely, it is not true that the majority of patients with leukoplakia eventually develop cancer, but the possibility is a real one. The estimated incidence of carcinoma in leukoplakia of the vulva varies from 20 to 50 per cent.[6, 7] It is the malignant potential of this disease that demands our best efforts toward its cure, or at least control.

Recent years have seen a variety of methods of treatment advised. These have included removal of external irritants, search for allergens, and eradication of foci of infection.[8] Dilute hydrochloric acid,[9] large doses of vitamin A,[10] oral and parenteral estrogens,[11] ACTH and cortisone[12] are but a few of the medications used. Topical applications have included bland ointments, vitamins A and D, fungicides, hydrocortisone, and many others.[8] Most authors have agreed that whereas all of these are occasionally helpful, they are rarely successful over a long period of time, and ultimately many of the patients will come to vulvectomy, either partial or complete.[13]

The present study was initiated by a chance observation. In 1951, we had under our care a 27-year-old nullipara with severe kraurosis. In addition to dyspareunia, she complained of intense pruritus, particularly in the area of the phimotic clitoris. As a preliminary procedure a dorsal slit and biopsy of the foreskin of the clitoris was done under local anesthesia. The patient was instructed to apply testosterone propionate in sesame oil to the clitoris in an attempt to induce a sufficient hypertrophy to make recurrence of the phimosis impossible. A few weeks later it was noted that not only had this been accomplished, but the skin about the clitoris appeared much healthier, thicker, and more pliable than the remainder of the vulva. Subsequently, testosterone was applied to the entire vulva with similar results and with complete amelioration of symptoms. Coitus was possible without pain for the first time in the three years of her marriage. It was found that Cinberg[14] had recommended in 1945 the use of testosterone propionate in a bland ointment base for the relief of pruritus in patients with leukoplakia and kraurosis in whom there was extensive atrophy of the vulvar skin. He reported good symptomatic results, but stated that he

was unimpressed with his follow-up biopsies, though he did not elaborate on this. Subsequently, an article appeared in an Italian journal by Varca[15] in which he reported a case of vulvar kraurosis with recovery following parenteral use of testosterone propionate.

Material

Since the initial observation, 27 white patients have been treated with topical testosterone. Table I shows the distribution as to primary pathologic diagnosis and menstrual status. Two patients with the histologic diagnosis of lichen sclerosus et atrophicus are included. We are not certain that these should be grouped together with patients with kraurosis and/or leukoplakia. These patients received symptomatic relief, but follow-up biopsies showed no appreciable histologic change. The remainder of the discussion will be limited to the 25 patients with kraurosis and/or leukoplakia.

TABLE I. ORIGINAL HISTOLOGIC DIAGNOSIS

	PREMENOPAUSAL	POSTMENOPAUSAL	TOTAL
Primary atrophy (kraurosis)	9	6	15
Leukoplakia	0	4	4
Primary atrophy (kraurosis) with leukoplakia	2	4	6
Lichen sclerosus et atrophicus	0	2	2
Total	11	16	27

The age of the patients was from 25 to 89 years. Three patients were referred from charity clinics, and the remainder were private patients. Two of the patients had diabetes mellitus, but were under good medical management. None of them had resistant or persistent bacterial, monilial, or trichomonal vaginitis. Several patients presented the findings of atrophic vaginitis, and these were treated with intravaginal stilbestrol in minimal doses. One interesting observation was that 13 of the 25 patients had areas of vitiligo in sites other than the vulva. None had any dermatitis involving other areas of the body. Twenty-four of the 25 patients were, or had been, married and, of these, 19 were parous. Nineteen of the patients had had previous treatment by ourselves or other physicians with the variety of the agents mentioned above, but no case had been satisfactorily controlled. Two patients had had previous vulvectomes—one for carcinoma of the vulva, the other for leukoplakia of the vulva. Both of these had postoperative recurrence of leukoplakia with pruritus.

Treatment

Once the diagnosis was established, several general measures of treatment were instituted. Any coexisting vaginitis was first cleared. The patients were cautioned to avoid the use on the vulva of anything other than the prescribed medication. They were also cautioned to avoid the use of tight-fitting nylon or rayon underwear. By holding moisture, it greatly increases the maceration and irritation of the vulva, though there was no allergy to nylon or rayon. Six of the patients presented a severe inflammatory reaction of the vulva with intense pruritus. These were initially treated with 0.1 per cent fludrocortisone acetate* ointment as an anti-inflammatory agent. Though it relieved the pruritus, it was observed actually to slow the healing process, and its use was discontinued as soon as the inflammatory reaction improved.

*The fludrocortisone acetate ointment (Florinef) was supplied by E. R. Squibb & Sons.

The patients were then instructed to apply to the vulva testosterone propionate in sesame oil* in a petrolatum base. Early in the study, liquid testosterone propionate in sesame oil, 25 mg. per cubic centimeter, was used with the instruction to massage 2 drops into the vulva three times daily. The combination with a petrolatum base was found to be more easily handled by the patient and gave the same results. Ten cubic centimeters of the testosterone propionate in oil, 50 mg. per cubic centimeter, was combined with 10 Gm. of white petroleum jelly. Control studies were done with both sesame oil and plain petrolatum, and these failed to give any symptomatic or objective improvement.

Dilute hydrochloric acid or large doses of vitamin A were not given, nor was oral or parenteral estrogen prescribed. The use of soap was neither encouraged nor discouraged, but the patients were cautioned to reapply the ointment following the bath. No lesions were excised except for biopsy. No surgery was done for contracture of the introitus. Four patients had incision of a phimotic foreskin under local anesthesia.

All 25 of the patients were followed for a sufficient period of time (3 months to 6½ years) to judge the efficacy of the treatment. Two of the 3 patients referred from charity clinics have not remained under treatment constantly. (These were being followed by a rapidly changing house staff as well as ourselves, and we found that their treatment was frequently changed between their visits to our office.) One of these patients has been lost to recent follow-up, but the remaining 24 still are under our observation.

Results

Without exception, all 25 patients received satisfactory symptomatic relief of their pruritus and irritation within one to 6 weeks. This was accompanied by healing of abrasions and fissures. There was an early noticeable improvement in skin texture and pliability. Grossly leukoplakic plaques have been seen to regress, though some did so slowly, requiring several months. Early in the study, treatment was omitted after 2 or 3 months. With only 2 exceptions (both young individuals who had intercurrent pregnancies), all patients had a return of symptoms and progression of the disease within one to 6 months after omission of the testosterone ointment. Continued therapy has been necessary. Despite this, however, some of the patients have had brief bouts of pruritus—a few following emotional upsets. It was necessary for 6 patients to use the anti-inflammatory fludrocortisone acetate ointment, 0.1 per cent, for a few days at infrequent intervals to prevent the trauma of scratching. Certainly, the avoidance of trauma is one of the cardinal principles of management.

None of the patients showed evidence of hirsutism, voice changes, or acne, even after prolonged therapy. All had some hypertrophy of the clitoris which persisted and prevented the recurrence of phimosis. Depigmented areas of the vulvar skin were not observed to have a return of pigment. There has been no allergy to the medication. Several of the patients developed what appeared to be an intertriginous dermatitis of the vulva during the early weeks of therapy. This disappeared under symptomatic treatment and did not recur with continued use of the testosterone ointment. When the perianal skin was involved, it responded more slowly than did the vulvar skin. It was impossible to ascertain whether or not this was due to the reluctance of the patient to apply the ointment in that area, or whether there was an actual difference in the response. All patients with dyspareunia were relieved. Some reported an increase in libido, but it was difficult to tell whether this was specific effect or the result of eradication of dyspareunia.

*A portion of the testosterone propionate in sesame oil was furnished by The Upjohn Company.

Follow-up biopsies have been obtained in only 13 of the 25 cases. The results are recorded in Table II. The histologic response is not nearly so dramatic as is the relief of symptoms. This is in accordance with Cinberg's findings.[14] The younger the patient and the less severe the disease, the more nearly complete was the histologic reversal. Because no private patient will submit to an unlimited number of vulvar biopsies, these have not been done on the remaining 12 who will be studied after longer periods of treatment. As so many of these patients have had symptoms for as much as 15 years prior to treatment, and as the course of this disease is known to be a prolonged one with many remissions and exacerbations, it seemed logical to delay follow-up biopsy on some of these patients for a longer period.

TABLE II. HISTOLOGIC DIAGNOSIS AFTER TREATMENT

7 primary atrophy (kraurosis)	
	2 essentially normal skin
	1 slight hyperkeratosis
	2 kraurosis with less acanthosis
	2 unimproved
2 leukoplakia	2 slight hyperkeratosis only, otherwise improved
4 primary atrophy with leukoplakia	
	1 essentially normal
	2 kraurosis without leukoplakia
	1 unimproved

Comment

Much has been written about the effects of parenteral and topical administration of the sex steroids on the skin. We have been unable to locate a report of a specific study of the effects of parenteral or topical androgens on the vulvar skin of the human. Several authors have shown that, besides having characteristic effects in sex areas, sex hormones, influence dermal connective tissue throughout the body.[16, 17] Salinger[18] showed that testosterone has a definite proliferative effect on human vaginal epithelium. Goldzieher and associates[19] found testosterone to have an effect on senile skin of either sex, with a definite epithelium-stimulating action and apparent production of papillary regeneration. Hooker and Pfeiffer[20] showed that, in the experimental animal, whereas injections of estrogen tended to cause a definite thinning of the epidermis within 2 months which became pronounced in 10 months, the injections of testosterone propionate induced epidermal proliferation. Likewise, simultaneous administration of estrogen and testosterone protected the rat against the thinning effect of the estrogen alone. Wells,[21] in a report on the use of large doses of testosterone for metastatic mammary carcinoma, noted a remarkable change in the skin texture of elderly patients, though he did not elaborate on this. Later, Wells, Lowery, and Cope[22] reported on the use of parenteral testosterone in the treatment of elderly patients with a variety of skin manifestations of what they called "metabolic deficiency." These patients were described as having extremely dry, nonelastic skin with keratosis, weeping dermatitis, and ulceration. They reported a marked improvement in all patients treated. Thus, we would expect testosterone to have a favorable effect on the histologic changes which occur in vulvar kraurosis and leukoplakia.

There is certainly no evidence that patients with these or any other of the atrophic skin changes have any deficiency of hormone production. Goldzieher and co-workers,[23] in a study of aging, failed to find any correlation between the

degree of atrophy and hormone excretion. Miller[6] reported no evidence of abnormally low levels of urinary 17-ketosteroids and gonadotrophin in his patients with leukoplakia and kraurosis of the vulva. From our observations, we too can only speculate as to whether the skin changes of the vulva are the local manifestations of some metabolic disturbance or merely the result of an external irritant. Miller[6] found a significant increase in urinary excretion of total organic acid in patients with leukoplakia of the vulva. This was determined in the search for a possible external chronic irritative factor in the causation of the vulvar reaction. It is entirely possible that testosterone does no more than stimulate the vulvar epidermis and dermis to proliferate and, in turn, become "tougher" and more resistant to external irritants.

Topical application provides a means of obtaining almost any desired concentration at the chosen site and reduces the unwanted systemic side effects to a minimum.[19] Petroleum jelly as a vehicle lends itself to ease of handling, and it has been shown that with vehicles of lower solvent power the absorption into the system is less, but the local effects are greater. The effect of parenteral administration of testosterone on the vulvar skin has not been investigated in this study. In at least one study on the effects of estrogen upon epidermal proliferation, it was shown that the result was diametrically opposite with systemic as opposed to topical administration.[24]

A study such as this obviously does not provide an answer to the problem of kraurosis and leukoplakia of the vulva. With this method of management, however, the following has been accomplished: first, satisfactory relief of symptoms without recourse to surgery, and, second, apparent arrest of the disease process. It is realized that this is a disease of prolonged course, and that malignant change must be regarded as an ever-present threat. Patient satisfaction has made it easy to keep an ordinarily difficult group under constant observation. It is our hope that this report will stimulate further study which will contribute to a better understanding of the disease.

Summary

A preliminary report is made on 25 patients with kraurosis and/or leukoplakia of the vulva treated primarily with topical testosterone propionate in a petrolatum base. Satisfactory symptomatic relief was obtained in all cases and has been maintained with continuous therapy. Exacerbation following omission of therapy has been the rule. A discussion of the possible mode of action of topical testosterone is included.

We wish to express our deep appreciation to Drs. G. Darrell Ayer and James F. Olley of the Crawford W. Long Memorial Hospital Department of Pathology for their histologic interpretations of the biopsy material.

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Discussion

DR. ROBERT N. CREADICK, Durham, N. C.—Drs. Richardson and Williams have presented an amazingly successful story in therapeutics. These patients are notoriously difficult to treat and everyone has been quite eager "to place the complaint in some other specialist's field" (Cinberg) whether it be allergist, dermatologist, or gynecologist. The authors state that all 25 patients were relieved of their symptoms within one to 6 weeks!

It is difficult to criticize an essay so well documented. Nine of their patients were younger, premenopausal women, which is a departure from the original premise of success in androgen therapy being based on correction of varying degrees of atrophy. One might also question the value of female circumcision or dorsal slit, since nearly all of these patients present a disease process over the entire area, not just one related to the size of the clitoral organ, masturbation, sexual excitement, or smegma.

Extremely interesting is their demonstration that there was no striking change in the histopathology of follow-up biopsies. It is unfortunate that follow-up biopsies were performed in only 13 of the 25 patients. My own feeling, however, has been that a scattering of lymphocytes in the dermal layer could hardly account for the clinical picture of misery and suffering most of these women exhibit. To paraphrase another investigator, "what clinician could be so scientifically detached as to permit his pruritis patient to go untreated while he obtained a series of biopsies?"

The only disturbing feature of this remarkable report is that all patients' symptoms returned within one to 6 months after the testosterone ointment was stopped. This makes one a little suspicious that the authors themselves have injected gentleness, persuasion, and sympathetic undertanding into their therapy—methods that aid tremendously in symptomatic relief. In previously published studies I have proposed that any patient with pruritis vulvae, young or old, with symptoms extending over a year or more, will have only temporary relief from any agent, unless accompanied by some type of psychotherapy. Several of their patients apparently had symptoms for almost 15 years.

If, as they stated, there were no arrhenomimetic effects other than hypertrophy of the clitoris, and if some patients have been followed for more than 6 years (3 months would not be long enough, for either therapeutic or steroid effect), then the method is justified. I, for one, shall try their method with perhaps a lower dosage ointment and without preceding fludrocortisone.

DR. ROBERT GREENBLATT, Augusta, Ga.—If the authors have obtained such good results and if their findings can be corroborated by other investigators, then they have helped fill a great void in our therapeutic armamentarium. To think that gentleness and the soothing sound of the physician's voice is all that is necessary to help some of these patients is less than the complete answer.

It may be that in using androgens the authors have stumbled on an important procedure. As I look back I remember that some years ago the effect of hormones administered locally on hair growth in experimental animals was studied in my laboratory. Part of the body was shaved and estrogenic or androgenic ointments were applied locally. Tissue sections were made afterward for histologic study.

One fact seemed apparent and that was estrogens induced a certain degree of atrophy of the sebaceous glands while androgens caused hypertrophy of these glands. The labia of the adult human female are rich in these glandular structures and it may be that hypertrophy of these glands increases sebum production which has a beneficial effect in atrophic dermatitis of the vulvae or kraurosis vulvae.

DR. NORMAN F. MILLER, Ann Arbor, Mich.—Because of a long-standing interest in this problem I am pleased to discover that we now have a therapeutic remedy which will relieve these women of their discomfort. I do not believe one has to justify trial with medication, so long as it seems to give relief. Neither do we need to justify it on the basis of the leukoplakia cancer potential. While not a fatal disease, it is a miserable one and one which I doubt we as males can fully appreciate because it does not appear to occur in males.

I am sorry that we did not have a chance to see what some of these lesions looked like. I am particularly disturbed by the fact that 15 of the 25 patients had cases of so-called primary atrophy. I am not just sure what Dr. Richardson means by this term, but to me primary atrophy in an elderly individual is not a disease at all. It is a normal manifestation of age. If he implies something more than age atrophy then the term primary atrophy is not properly used here.

The follow-up period of 3 to 6 years is fine, but I am not sure how many of these individuals were followed for 6 years and how many for only 3 years.

This is either going to be one of the very important therapeutic advances of the day or else it is going to find itself along with many other one-time popular methods of therapy collecting dust on our shelves.

I am a bit surprised that the testosterone ointment gives the relief without side symptoms when it is sufficient to produce hypertrophy of the clitoris. I can understand that in postmenopausal women one might not have much in the way of side symptoms, but in the younger woman some interference with the normal menstrual cycles would perhaps be expected.

This ointment contained a petroleum jelly. We have tried just about everything on our patients with leukoplakia and, of all the things used, patients speak with perhaps the slightest degree of favoritism of petroleum jelly. Certainly, it is not a cure at all. It does no more than perhaps coat the area and thus reduce local irritation from moisture, etc.

I would like to believe that testosterone ointment is a systematic answer to this very troublesome condition, but I must confess that I hear of this with some degree of doubt.

DR. JOHN PARKS, Washington, D. C.—I disagree a little with Dr. Richardson about definitions. I think the best term which has ever been applied to this disease is chronic atrophic dermatitis of the vulva. It is sometimes with kraurosis, sometimes with leukoplakia, and sometimes with both. It is usually with both.

We had a similar chance experience with testosterone some years ago but did not follow up on it. I recall giving a 90-year-old woman with residual itching following vulvectomy, testosterone by mouth. The itching disappeared. We thought she was a little disoriented so we did not make a very accurate observation, not nearly as accurate as has been reported here today.

It has been stated that everything has been used on the vulva to cure this disease. We have recently had an experience with a woman who said that the only thing that ever cured the itch on the back of her head was ultraviolet light. We encouraged her to take

the same treatment to the vulva. The ultraviolet light cured that area of her itch. It only points out the importance of very careful history taking. If you ever find anything which helps these patients, use it in the right area.

I agree with Dr. Richardson that the perianal skin area is one of the last areas to heal. It has the least efficient blood supply.

I am surprised and a little bit disappointed also that biopsies did not show histologic changes because then we would have proof of the efficacy of treatment. As a topical agent, testosterone may go down in medical history as another itch-relieving agent.

I wonder about the continued use of such a potent steroid applied to a potentially malignant epithelial area of disease. I hope that Dr. Richardson will follow his patients with great care with regard to the possibilities of malignant change. Also, I would like to ask if he told his patients that they were being treated with male hormone.

DR. RICHARDSON (Closing).—In reply to Dr. Creadick's and Dr. Miller's question regarding the period of observation, only 3 of these patients have been observed for periods less than one year. Twenty-two have been under observation for over one year.

We did control studies with petrolatum and sesame oil. We were not impressed that it granted any particular relief to the patient, though admittedly it was not carried out for a long period of time.

As for histologic change under treatment, we did not mean to imply that there was no histologic response. Though all of the patients had complete clinical relief, the histologic response was not nearly so dramatic. However, roughly one third of the patients subjected to biopsy showed a complete reversal histologically; one third showed a regression; and one third showed essentially no change.

We did not tell these patients they were being treated with the male hormone.

Finally, let me reiterate that we do not feel this to be the final answer to kraurosis and leukoplakia of the vulva. We are not trying to sell an ointment with testosterone in it. In our experience, however, this treatment has proved to be more effective in control of the patient's symptoms than anything else we have tried. We hope that our observations will be of some value to the clinician. Above all, we hope that this report will serve to stimulate additional basic research into this problem.

AN INTEGRATED PROGRAM OF GYNECOLOGIC RESEARCH IN A COMMUNITY HOSPITAL*†

SAM WESLEY DENHAM, M.D., AND
ALVAN G. FORAKER, M.D., JACKSONVILLE, FLA.

(From the Baptist Memorial Hospital)

THERE is now current an avid interest by the general public in scientific research. For this reason, we feel it worth while to relate our experiences in an integrated program of gynecologic research in a general community hospital without university affiliation, located in a city without a medical school. The intention is not to ascribe unusual merit to our program, but rather to show what can be accomplished in a favorable environment under these circumstances.

The program has served several rewarding purposes. The Departments of Pathology and Gynecology and Obstetrics have worked intimately on the projects. The facilities of each have been coordinated to make the research program possible. The younger, qualified practitioners in the community have developed a great interest. It has stimulated more reading of basic research material and directly influenced the rapid growth of our library facilities. The Research Committee, a new hospital committee, was formed to advise and coordinate it with the various other hospital functions.

We have found that a research program in a hospital improves patient care and medical education. Another rewarding aspect of the program is in the attraction of high-caliber physicians to our attending and resident staffs. Research greatly strengthens our laboratory personnel and facilities, helping us to bring to our patients benefits from medical advances made elsewhere. Young people in our community are urged to see the hospital and research facility. This, we hope, will stimulate interest in scientific or medical careers.

We have been fortunate that the grants to continue this research have been favorably considered by the National Cancer Institute. In addition, the Damon Runyan Memorial Fund has provided an interference-contrast microscope to facilitate the investigation of nuclear mass and allied measurements.[1] The American Cancer Society has contributed special training and courses for certain of the technical assistants in the program. This has applied particularly to medical illustration.

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A special research laboratory has been developed in the hospital with the grant funds. This provides working space for four persons. The animal room and operating area are in an adjoining partitioned zone. At this time, we have six technicians participating in research, some partially or fully subsidized by grant funds.

Specific Projects

The first phase of the research program in gynecology deals with the continued investigation of new techniques in the study of carcinoma of the uterine cervix. We have been fortunate in being able to continue the histochemical studies of the cervix which began in 1949, when one of us (S. W. D.) was in residency training. These studies involve specific histochemical techniques which have been outlined in detail elsewhere.[2]

Understanding the growth patterns of the normal cervix has become important in evaluating the abnormal growth behavior of malignant cervical tissue. Histochemical reactions are now known to be reliable indicators of these growth processes. Normal and metaplastic cervical epithelium as well as preinvasive and invasive carcinoma of the cervix have been studied.

These various cervical tissues have been submitted to a battery of histochemical techniques. Some of these (succinic dehydrogenase and endogenous reductase, alkaline phosphatase, phosphamidase, protein-bound sulfhydryl groups) demonstrate chemical substances important in various phases of cell growth, without specificity for squamous epithelium. Others (glycogen, protein-bound disulfide groups) are in some degree indicative of maturation of squamous cells. Succinic dehydrogenase, endogenous reductase, alkaline phosphatase, phosphamidase, and sulfhydryl groups were demonstrated in proliferating squamous cells, whether from the basal layer of normal mucosa, in metaplasia, or carcinoma. Disulfide groups and glycogen were found in maturing squamous cells in normal mucosa, and in keratinizing carcinoma cells.

Thus the histochemical reaction patterns were not diagnostic of the neoplastic state, but indicated growth or maturation of the squamous cells. The summation of these histochemical techniques indicates that the chemical properties of these cells parallel their microscopic appearance and their growth potential, namely, that there is a gradual transition from normal mucosa to metaplastic epithelium, to atypical hyperplastic epithelium, to intraepithelial carcinoma, to invasive squamous-cell carcinoma.

One facet of our present program of investigation is concerned with ovarian tumorigenesis. Selected female Wistar rats are used. Cotton threads containing 20-methylcholanthrene in beeswax are implanted in the ovary of the rat. A control containing only beeswax is placed in the opposite ovary. It is planned to use various hormone substances as additional stimulants as this particular phase of the research develops.

The next area of investigation will be concerned with the aging process in the human ovary. This is to be correlated specifically with the endometrium and breast tissue.

Summary

A review of our experiences in an integrated program of gynecologic research in a community hospital is presented. We believe that such a program has value, that it can produce worthwhile, if modest, investigations.

Our experiences with histochemical changes in the cervix are outlined. Our present program of investigation into ovarian tumorigenesis, as well as the aging process in the human ovary, is mentioned to illustrate the scope of this program.

The technical assistance of Miss Gladys Clark, Mr. Gene Nabi, Mrs. Mercee Evans, Mrs. Elizabeth Anderson, and Mr. Robert Gutman in this program is gratefully acknowledged.

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Discussion

DR. E. D. COLVIN, Atlanta, Ga.—In the assessment of the contribution of any hospital to medical science, resident training, and patient care, the role of scientific research has come to occupy a position of primary importance. In the university-affiliated hospital, research is mandatory and consumes much of the effort and time of the staff. The product of its research activity contributes to the stature of the hospital and enhances its prestige as a training and treatment center. As a result the position of the university-affiliated hospital has become fixed at a high level, and justifiably so. This cannot be said of the community hospital, yet "Approximately 40 per cent of patients in the United States are cared for in hospitals whose bed capacity is 200 or less. In New England almost half of the hospital beds in the non-university affiliated group are in hospitals whose capacity is between 200 and 300" (Burgess, A. M.: J. A. M. A. 161: 24, 1956).

In the fields of resident training and research these institutions have been found delinquent, even though staffed by adequately trained physicians capable of far greater endeavor than that of a clinician alone. The Joint Commission for the Accreditation of Hospitals has performed an excellent service in elevating the standards of education in this community type of hospital, yet, because of a lack of facilities, leadership, and effort, an enormous volume of material which lends itself well to clinical investigation and research continues to be lost.

If clinical research is to become a function of the community hospital, then preparations and plans must be made to carry it beyond the capabilities of the clinical practitioner and observer. Rarely is he competent in a second field. It is unfortunate that there are so few physicians of ambivalent interest and ambition as regards investigation and the practice of medicine. The work must devolve upon, or have assistance from, the biochemist, the microbiologist, the physicist, the pathologist, the cytologist, and others as components of a committee made up of self-assigned members, as suggested by Drs. Denham and Foraker. Otherwise, failure is the reward.

With able leadership and monies now available from endowment, educational and Government research funds, and other sources, the opportunities for clinical research in community hospitals are now beyond the dreams of what might have been considered possible a few years ago. In order to secure leadership, it is necessary for our Committees on Credentials to give greater recognition for staff membership to those applicants who have special training and inclination toward clinical research. In this field the community hospital is often short and handicapped in its program.

DR. THADDEUS L. MONTGOMERY, Philadelphia, Pa.—Ordinarily there emanate a large number of young men from medical schools who are interested in science, and it is unfortunate that facilities for science research are cut off when they reach the level of internship or of practice. Laboratories of this kind in close integration with the departments of obstetrics and gynecology will further clinical research in this field.

What has been said also applies to our teaching institutions. I am closely in touch with this problem at the present time as chairman of a department to which laboratory facilities have been recently added. We are very happy about this new facility. Our concepts of what constitutes basic research are changing. In the past we have looked upon basic subjects as physiologic chemistry, bacteriology, anatomy, pathology, etc. Actually, what was once considered basic research is moving into the respective clinical departments. The really basic sciences now are chemistry and physics.

To prepare them properly for medicine and medical science of the future, mathematics, physics, and chemistry must be strongly inculcated on our premedical students, and their scientific activities must continue through internship and practice.

DIDELPHIC UTERUS WITH CARCINOMA IN SITU OF BOTH CERVICES*

ROSCOE L. WALL, JR., M.D., WINSTON-SALEM, N. C.

(From the Department of Obstetrics and Gynecology of the Bowman Gray School of Medicine)

UTERINE anomalies and carcinoma in situ of the cervix are no longer considered rare; however, a combination of these two entities is very rare.

A review of the literature up to 1957 discloses 12 cases of anomalous uteri with carcinoma involving the fundus[1, 2] and 19 in the cervix.[3, 4] Of the latter 19 cases, only one was found in which carcinoma occurred in two cervices. As reported by Gauwerky[4] in the German literature in 1955, it presented "a double squamous cell carcinoma in a patient with a double uterus and subseptate vagina." Gauwerky stated that "a metastasis from one os to the other seems entirely unlikely" and described a unique method of radium therapy followed by deep x-ray with a successful follow-up for one year.

To the best of my knowledge, the following is the only other case of carcinoma in two cervices.

A 35-year-old white, married, gravida ii, para ii, was admitted to the North Carolina Baptist Hospital on Oct. 14, 1956, for investigation of a highly suspicious vaginal smear report. The family physician reported that 3 weeks prior to admission examination revealed an eroded, bleeding cervix. Vaginal and cervical smears were obtained and the bleeding areas were electrocauterized.

The patient had noted intermenstrual spotting for one year. It had become more profuse 2 months prior to admission and was accompanied by postcoital bleeding. Otherwise, the menstrual history was negative. The past medical and surgical history was irrelevant except for an appendectomy at the age of 14 years. The family history showed that the patient's father had received x-ray therapy for a skin cancer in 1945, with no sequelae. She had 2 term pregnancies with uncomplicated labor and delivery of normal male infants now 14 and 13 years of age. Routine physical examination and basic laboratory data were negative, except for a hemoglobin concentration of 10 Gm. per cent. Therefore the patient received 500 c.c. of whole blood prior to definitive treatment.

Sterile pelvic examination under anesthesia was accomplished on October 15, the day after admission. The external genitals appeared normal. Bimanual examination revealed an enlarged, roughened, only slightly movable cervix. The anterior fornix felt indurated and scarred. The uterus was normal in consistency, slightly retroverted, and symmetrically enlarged to about 14 by 12 by 7 cm. A deep cleft was felt in the midline, dividing the fundus into separate equal parts. The adnexa were ill defined, with no palpable masses. Speculum examination showed healthy vaginal mucosa with fair support. The anterior and posterior vaginal walls presented redundant flaps of mucosa, apparently the remnants of a septum dividing the entire vagina into two equal parts. The cervix appeared enlarged to

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about 6 by 5 cm., and was divided by a septum into equal parts, with a reddened and granular appearance distributed circumorally and most prominent posteriorly. By separate sounds, a septum was found to be dividing the cervix and fundus throughout. Both endometrial cavities were 7 to 8 cm. in depth and yielded a moderate amount of normal curettings, separately obtained and marked for pathologic examination. Cold-knife conization of each cervix and two biopsies of the intervening septum above the areas of conization were isolated and designated as such for pathologic examination. They were all similar on microscopic examination and contained intraepithelial squamous-cell carcinoma (Figs. 1 and 2). The curettings revealed secretory endometrium.

Fig. 1.

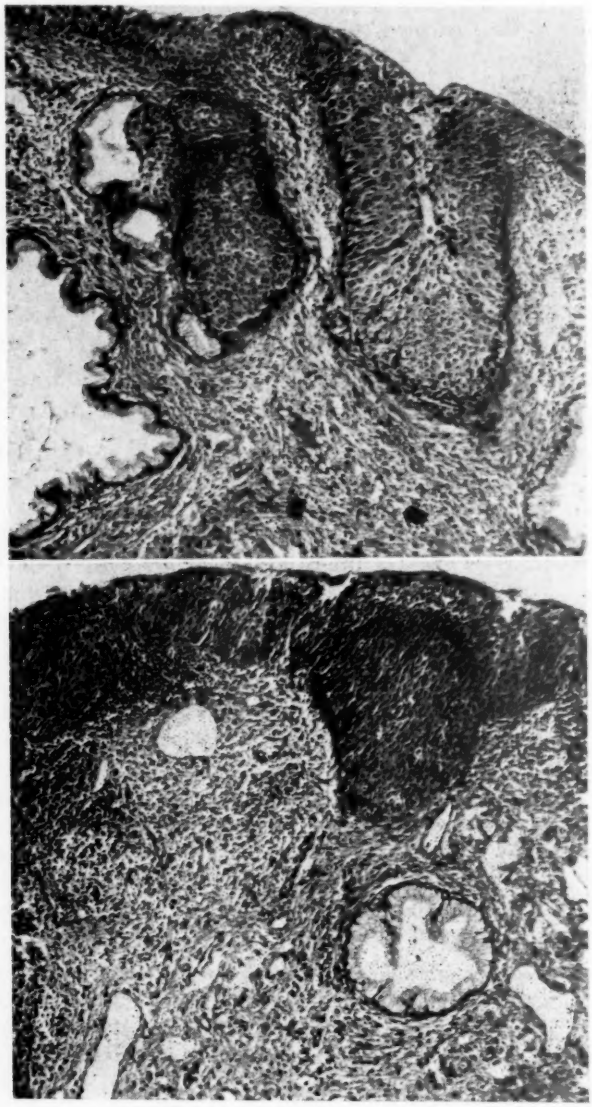

Fig. 2.

Fig. 1.—Conization specimen from right cervix of didelphic uterus. Intraepithelial squamous-cell carcinoma. (Hematoxylin and eosin. ×124; reduced ⅙.)

Fig. 2.—Conization specimen from left cervix of didelphic uterus. Carcinoma in situ, similar to that in opposite cervix in Fig. 1. (Hematoxylin and eosin. ×124; reduced ⅙.)

Because of the anomalous genital tract, urinary pyelograms and chest x-rays were obtained and were normal. Postoperatively the patient did well, except for a repeat hemoglobin determination of 9.3 Gm. She therefore received 500 c.c. of whole blood on the second and third days.

On the fourth postoperative day, a total abdominal hysterectomy was performed. The abdominal organs were found to be normal. The uterus presented two separate fundi with an intervening rectovesical ligament or septum just above the cervix. One normal-appearing tube and ovary extended from the lateral cornu of each uterus. Both cervices and fundi were removed in toto, including a vaginal cuff approximately 3 cm. wide (Fig. 3).

Microscopic sections revealed residual intraepithelial carcinoma in the left cervix only. The remainder of the uterus presented no pathologic abnormalities.

The patient made an uneventful recovery. Follow-up examinations at 2, 6, and 12 months were all negative. The most recent examination was made on Jan. 10, 1958, 15 months after operation. The patient was in good health and without complaints. The vaginal mucosa appeared healthy and a vaginal smear for cytologic study was negative.

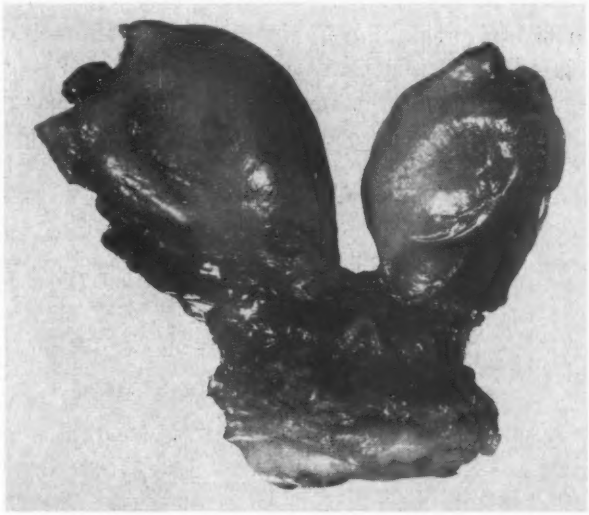

Fig. 3.—Posterior aspect of intact didelphic uterus. Carcinoma in situ of each cervix. (One-third actual size.)

Comment

To the best of my knowledge this case brings the reported number of cervical cancers in anomalous uteri to a total of 20. It is the second of these 20 occurring simultaneously in the two cervices of a uterus didelphys and the first to present carcinoma in situ. These figures are small and limited, but it is interesting to note that the ratio of 12 cases of fundal cancer versus 20 cases of cervical cancer in anomalous uteri is much higher than that in the normal genital tract.

The relationship of cancer to the anomalous uterus has yet to be established. Many investigators believe that malformation might be an etiological factor in carcinoma. Von Franqué,[5] however, refuted this belief in his excellent review of 22 cases from 1777 to 1930. Others believe their coexistence is only coincidental. Yet 2 identical cases of didelphic uteri, septate vaginas, and carcinoma, possibly of double primary origin, occurring in separate cervices

makes one wonder if more than coincidence is involved. Their amazing similarity demands attention. Gauwerky believed that his case presented separate carcinomas in each cervix rather than a single process. In the case presented, one can only speculate as to whether one or two separate carcinomas were involved. If only one was present, it must have spread extensively throughout both cervices. If so, this case presents a carcinoma in situ with a bizarre versatility. Neither hormonal nor genetic factors were believed to be responsible in this case.

In retrospect it is regrettable that both cervices were cauterized and that separate cytologic smears were not obtained from each cervix prior to operation, for they might have disclosed more information. One can only hope that similar cases will be found and reported to help clarify these unusual problems.

Summary

A case is reported of carcinoma in situ occurring in each cervix of a didelphic uterus, associated with a septate vagina and rectovesical septum. The lesions were suspected by cytologic smears, diagnosed by separate conizations, and treated by abdominal panhysterectomy.

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CARCINOMA IN SITU OF THE VAGINA SUBSEQUENT TO HYSTERECTOMY FOR CARCINOMA IN SITU OF THE CERVIX*

HARVEY C. MAY, M.D., CHARLOTTE, N. C.

(From the Presbyterian Hospital)

MUCH has been written on the subject of noninvasive malignant epithelium of the cervix since it was first described by Sir John Williams eighty odd years ago. Its acceptance as a stage of true carcinoma of the cervix is by no means unanimous. The diagnosis and treatment are even less stereotyped.

Comparatively little has been written about the preinvasive lesions of the vaginal mucosa and, with a few exceptions, little emphasis has been placed on the follow-up after definitive treatment for carcinoma in situ of the cervix.

A relatively small number of cases in which the preinvasive lesion of the cervix recurred in the vaginal mucosa following hysterectomy has been reported. The incidence of the concomitant occurrence of these cervical and vaginal lesions is probably not high. Blumberg and Ober[1] reported a case in 1953 somewhat similar to this one. From the Massachusetts General Hospital and the Vincent Memorial Hospital, Graham[2] reported 5 cases of vaginal recurrence of in situ carcinoma among the 75 patients treated by hysterectomy in the 8 year period of 1939 to 1947. Fennell,[3] in 1956, reported only 118 cases of cervical in situ cancer over a 26 year span at the Massachusetts General Hospital, and only 3 of the patients had a recurrence of tumor in the vagina after total hysterectomy. One had an in situ lesion 10 years after extirpation of the uterus, the second, 6 years after extirpation, and the third had an invasive carcinoma, not pertinent to this discussion since residual tumor remained following the original surgery. Of 275 patients with Stage 0 cancer of the cervix treated by hysterectomy at Duke Hospital,[4] only 2 patients later showed invasive squamous-cell cancer of the vagina. Carter[5] in 1957 presented the results in 373 patients studied. All 8 cases of invasive carcinoma and involvement of the vagina were excluded from this discussion as further study revealed an incorrect diagnosis of in situ carcinoma and there was no evidence that a noninvasive lesion progressed to an invasive state. In one patient[6] there did develop an intraepithelial cancer in the vagina which, prior to definitive treatment, became invasive in several sites.

The following is one of 5 cases to be reported later by the essayist. All were diagnosed with the aid of Papanicolaou smears studied by the Regional Cytology Laboratory in Charlotte, N. C.

*Presented at the Twentieth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hollywood, Florida, Feb. 1 to 5, 1958.

Case Report

P. H. W., a 56-year-old white widow, gravida iii, para iii, was seen for routine gynecologic consultation on April 27, 1954, at the request of her internist, who had hospitalized her for evaluation of multiple somatic complaints. The positive gynecologic points of history were mucous leukorrhea of 3 weeks' duration with an associated sense of weight in the pelvis. There had been no bleeding in the 5 years since the menopause, which had been marked by menorrhagia and vasomotor disturbances. She had been treated with multiple injections of estrogen by her family physician.

Initial Pelvic Examination.—The positive pelvic findings were a minimal asymptomatic cystocele and circumoral erosion of the cervix. This was not marked, but did bleed on contact.

Routine Papanicolaou smears taken from the cervix were reported by the cytology laboratory to be Grade 4 positive. On April 30, 1954, a cold-knife conization of the cervix was done. The entire cervical biopsy was embedded in the form of serially made sagittal blocks and reported by H. Lee Large, Jr., pathologist at the Presbyterian Hospital as "intraepithelial stratified squamous epithelial cell carcinoma of the cervix. The lesion is observed in each of the blocks studied, and the entire squamocolumnar junction of the cervix had been embedded. It extends to the lateral margins of resection and into the lumina of underlying glands. However, even here, it appears to be confined within the basement membranes" (Fig. 1).

The usual period of healing, prior to hysterectomy, was sacrificed because of the patient's emotionalism, and on May 4, 1954, a total abdominal hysterectomy and bilateral salpingo-oophorectomy were done. The usual cuff of vaginal mucosa was excised with the cervix. The pathologist reported, "Postoperative state of cervix: circumferential biopsy. Residual tumor has not been identified." The postoperative course was essentially uneventful.

Initial Follow-up.—Approximately 6 months following discharge from the hospital, on Dec. 9, 1954, routine Papanicolaou smears from the vaginal vault showed atypical cells. The vagina appeared grossly normal and the patient was symptom free. Repeat smears on Jan. 3, 1955, were reported as suspicious. They were still suspicious on March 31, 1955. The vagina continued to appear perfectly normal. On May 30, 1955, the vaginal smears were reported to show no tumor cells. On Oct. 3, 1955, however, the cytologist reported atypical cells. It was not until April 18, 1956, that cancer cells were found on the smears. This was 2 years after hysterectomy.

Second Hospital Admission.—The patient was readmitted to the Presbyterian Hospital on May 6, 1956, and a 2 cm. strip of the entire upper end of the vaginal vault was excised, to exclude the possibility of invasive carcinoma. This was reported by the pathologist as "portion of vagina with chronic histologically nonspecific inflammation, and fragments of anaplastic epithelium readily compatible with in situ epidermoid carcinoma. Due to the nature of the biopsy, the precise derivation of these fragments is not determinable. A careful follow-up and future Papanicolaou smears are advised. Whether the lesion is completely removed cannot be determined in the material at hand" (Fig. 2).

The postoperative course was again uneventful and the upper end of the vaginal vault healed cleanly. Six weeks later, vaginal smears revealed cancer cells. Again the vaginal vault appeared to be normal. An attempt was made to stain the upper part of the vaginal vault with Gram's iodine, but this was unsatisfactory. Multiple Papanicolaou smears were taken from the top of the vaginal vault with the use of a knife point and each slide was carefully labeled to indicate the point in the vaginal vault from which it was taken. Only those areas on the left end of the linear scar revealed cancer cells. By this method, a second attempt was made to localize an area of abnormality in the mucous membrane, and again the

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Fig. 1.—Circumferential cold knife biopsy of cervix on April 30, 1956, showing in situ epidermoid carcinoma.

Fig. 2.—Section from vaginal biopsy on May 6, 1956, showing one of two minute foci of atypical epithelium.

Fig. 3.—Section of vaginal tissue removed on Nov. 18, 1956, showing focus of in situ carcinoma.

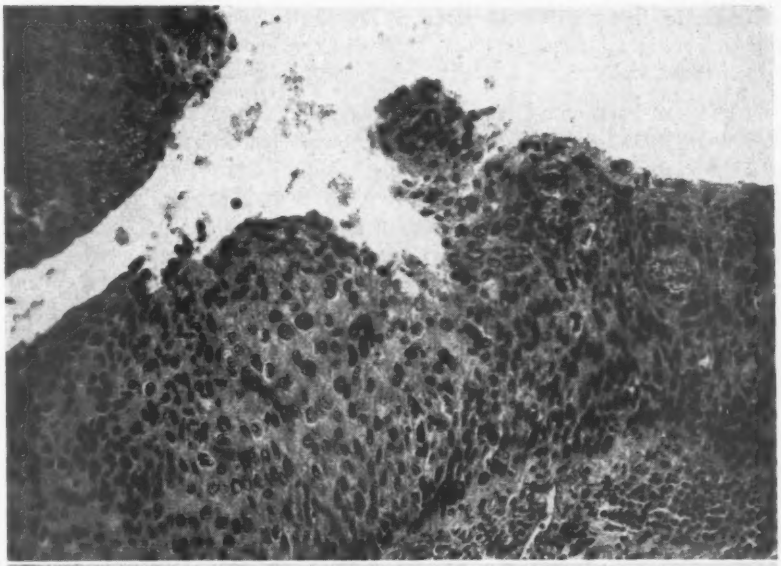
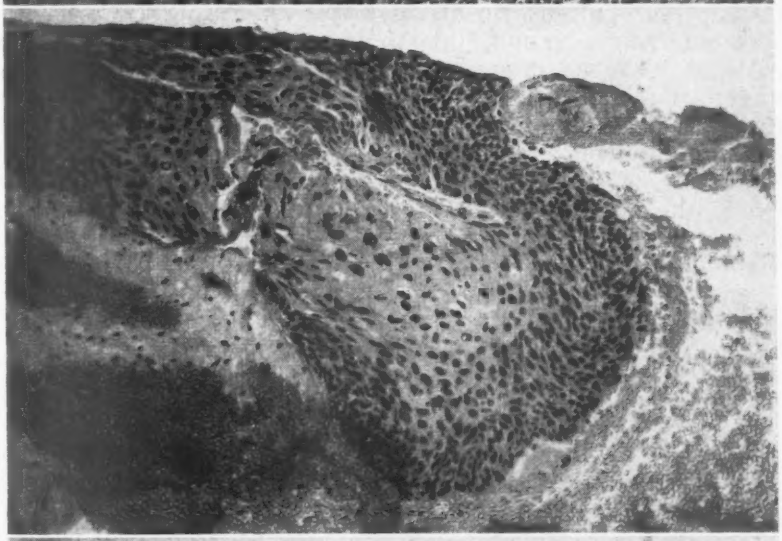


Fig. 1.



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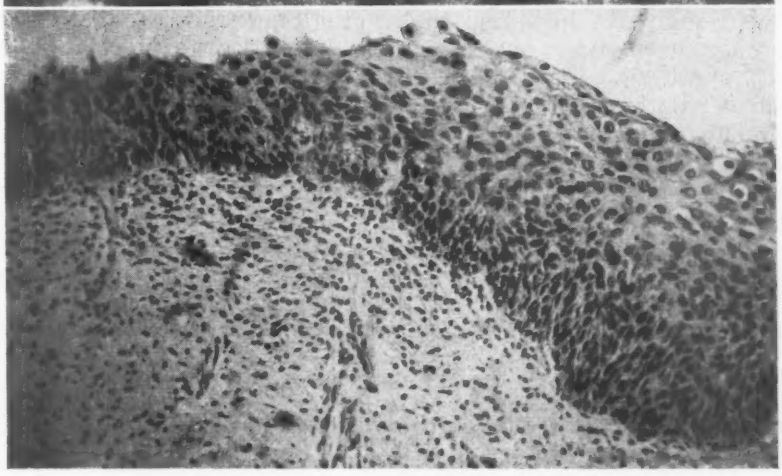

Fig. 3.

Figs. 1-3.—*For legends see opposite page.*

smears taken from the left side of the apex of the vaginal vault adjacent to the line of the healed incision were highly suspicious or reported to show cancer cells. A third series of smears confirmed these findings.

Third Hospital Admission.—The patient was hospitalized for the third time for this condition on Nov. 18, 1956, on this occasion at the Mercy Hospital. The entire vaginal mucosa was extirpated in two pieces of tissue. The pathologist, Dr. Thomas H. Byrnes, reported, "Sections from the left side contain a relatively small area covered by an altered type of stratified squamous epithelium. This epithelial layer is very thick and composed of irregular cells of variable size and shape containing large hyperchromatic nuclei with several atypical mitoses. These cells are somewhat disorderly in arrangement; however, they appear to be limited at the base by a basement membrane. Impression: Carcinoma in situ of vagina" (Fig. 3).

Healing was uneventful and the patient continued to remain free of pelvic complaints over the 14 months following this operation.

Comment

Complete extirpation of the vagina at the second admission was not done because of the possibility of invasive carcinoma. Colpectomy would have negated the possibility of applying direct radiation. Because of the age and marital status of the patient, no attempt was made to preserve a functional vagina. This, of course, is not difficult in a young patient with the use of vaginal prosthesis. Carter[5] and his group at Duke have repeatedly emphasized the importance of follow-up in those patients who have had definitive treatment. Meigs,[7] too, has found it essential to "follow patients on every visit to the clinic with vaginal smears." He stated that in this way they "have picked up numerous recurrences." He advocates routine staining of the vagina with iodine prior to the operation and removal of all unstained areas along with the uterus. For patients who continue to show neoplastic cells in the vaginal vault, partial colpectomy for diagnosis should be routinely performed. Vaginal smears will detect recurrence long before it can be proved histologically or even suspected clinically.

The taking of a wedge of vaginal mucosa at the time of hysterectomy should not give a false sense of security to the operator. It has been pointed out that there is a pronounced tendency to overestimate the size of the cuff being removed. The tissue stretches and the pathologist reports a very narrow wedge of vaginal mucosa, which the operator had felt, with pride, to be a generous cuff. Thus, the vagina may be incised across a line of malignant epithelium, leaving neoplastic tissue intact.

The occasional case in which the vaginal smears are negative following operation, only to become positive later, suggests the most intriguing but speculative hypothesis of multiple foci of carcinoma. Stoddard[8] had aroused the interest of us all with the so-called "field response" of carcinogenesis. It is to be admitted that multiple carcinomas may occur in one patient, probably on a basis of susceptibility, but the more likely possibility of cancer in the closely related tissues of the cervix and upper vagina is thought provoking. As the squamous epithelium of the cervix and the upper third of the vagina are derived from Müllerian epithelium, the still unknown carcinogenic factor might be expected to affect one area of the epithelium, if it affects the other. It is just this possibility that necessitates adequate follow-up even in patients in whom a very wide vaginal cuff has been excised with the cervix.

Summary

A case of carcinoma in situ of the vagina following hysterectomy for in situ carcinoma of the cervix has been reported and a brief discussion of the

incidence and treatment given. The extirpation of a wide band of vaginal mucosa at the time of hysterectomy, to avoid the possibility of direct extension to the vagina, is emphasized. A plea is made for careful follow-up on all patients with carcinoma in situ of the cervix with or without definitive treatment. Cytologic smears offer the most successful means of follow-up and, should they reveal cancer cells, partial colpectomy is an easy and necessary procedure.

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SPONTANEOUS REGRESSION OF PULMONARY METASTASES FOLLOWING HYSTERECTOMY FOR CHORIOCARCINOMA*

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ALTHOUGH approximately 2,500 cases of choriocarcinoma have been reported, we felt that this case would be of interest in that pulmonary metastases disappeared following removal of the primary tumor. Also, it presented a problem in microscopic diagnosis, as do many lesions of the chorion. This case is not unique, since similar ones have been reported. Savage[1] reported trophoblastic lesions in the lungs which persisted over a long period of time and finally completely disappeared. Schulze[2] reviews a case of "malignant mole" with "round lesions in the lungs" which completely regressed following hysterectomy and x-ray therapy. Maier and Taylor[3] have reported a lobectomy for metastatic choriocarcinoma with recovery. Bradawil,[4] from the literature, reviewed fifteen cases of hydatidiform mole, all followed by possible pulmonary metastases and terminated by healing. Mazer[5] and Peightal[6] cited cases of pulmonary metastatic choriocarinoma of the lung treated by pneumonectomy. One month later, a metastatic lesion appeared in the other lung which disappeared after nitrogen mustard therapy.

Any study of this subject is facilitated by the observations and comprehensive reviews of the literature published by Marchand,[9] Mathieu,[9] Novak and Sech,[10] Hertig and Sheldon,[11] Hunt, Dockerty, and Randall,[12] Park and Lees,[13] Hertig and Mansell[14] and others.

Case Report

C. G., a 21-year-old gravida ii, para i, was first seen on Oct. 1, 1955, because of amenorrhea and symptoms of early pregnancy. She began to bleed on October 22, but the uterus progressively enlarged. On December 6, she expelled a mole and dilatation and curettage was done. The pathologist reported a hydatidiform mole with no evidence of malignancy (Fig. 1).

Normal menstrual periods followed and pregnancy tests done at monthly intervals were consistently negative. In June, 1956, she was told that she might again attempt to conceive. A normal period began on June 2, 1956. On July 6, irregular bleeding began and continued. Pregnancy test on August 21, was negative, but, because of irregular bleeding, the uterus was again curetted. The microscopic diagnosis was nonsecretory endometrium, decidual tissue with marked trophoblastic proliferation. This lesion did not appear to be malignant (Fig. 2).

*Presented at the Twentieth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hollywood, Florida, Feb. 1 to 5, 1958.

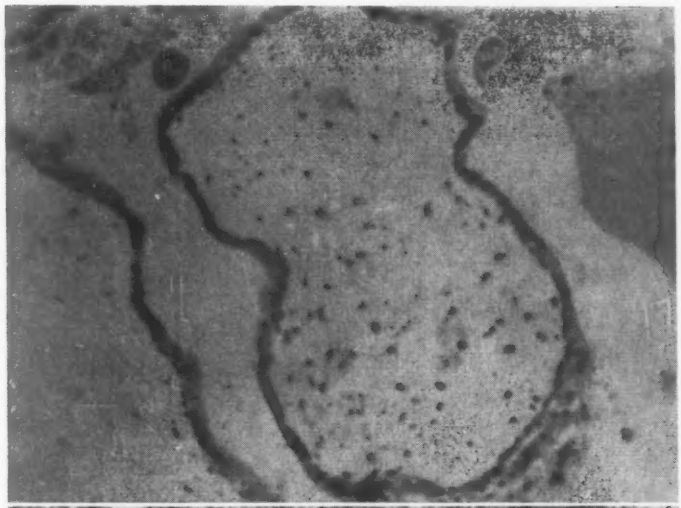
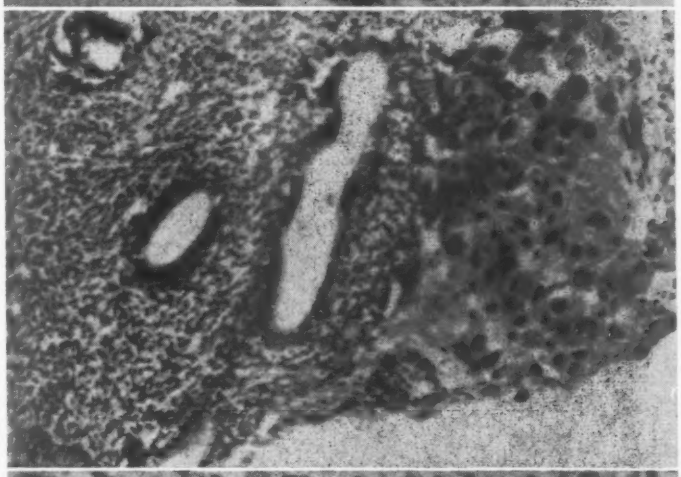


Fig. 1.



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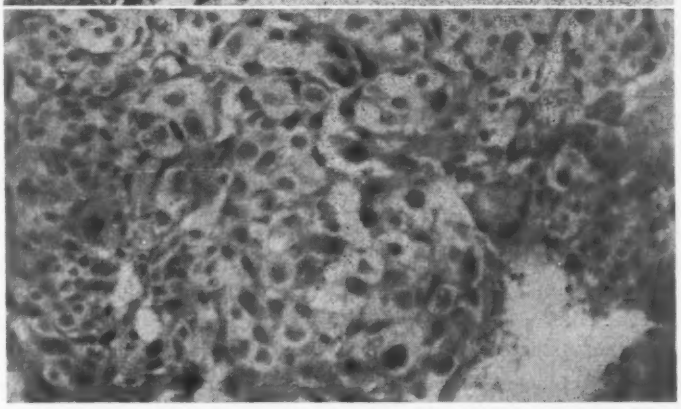

Fig. 3.

Fig. 1.—Benign mole showing cystic accumulation of interstitial fluid within the villus and normal-appearing trophoblast.

Fig. 2.—Nonsecretory endometrium and trophoblastic proliferation.

Fig. 3.—Proliferative trophoblastic cells, markedly bizarre pattern.

She began what appeared to be a normal period on Sept. 30, 1956. It was quite heavy, followed by spotting which continued for several days. A pregnancy test on October 16 was reported as positive; therefore a rather vigorous curettage was performed and the pathologist reported several changes which were suggestive of malignancy (Fig. 3).

However, this patient felt quite well and gained 15 pounds. Her hemoglobin remained quite satisfactory, between 12 and 13 Gm. On October 30, a febrile illness with chills and generalized aching developed. Examination was essentially normal except for a few fine râles heard on the left side of the chest. X-ray examination of the chest showed several faint nodular densities at the level of anterior interspaces 2, 3, 4, and 5 on the left, and 2 and possibly 3 on the right. Neurological examination showed blurring of the optic discs. The patient's general condition improved, and as there was still some question as to the pathological diagnosis, sections were sent to several pathologists for an opinion.

The patient then developed cough and hemoptysis. There were mild abdominal discomfort and pink vaginal discharge but no active bleeding. Pelvic examination on Nov. 21, 1956, showed the uterus to be enlarged, soft, and quite nodular, which was a marked change from previous examinations. Therefore, she was prepared for surgery. X-ray examination on November 21 showed widespread multiple nodular densities throughout both lungs, representing widespread metastatic neoplastic disease (Fig. 4). However, it was felt the patient should be operated upon in an attempt to prevent early death from uterine hemorrhage and to prevent secondary anemia which would make the patient more susceptible to intercurrent infection.

On November 28, a total hysterectomy and bilateral salpingo-oophorectomy were done. Some free blood was encountered in the abdomen, which originated from a perforation of a malignant nodule on the uterus at the left cornu. Exploration of the abdomen revealed a normal liver and omentum. The uterus was grapefruit size, containing several blue nodules which were quite friable. There was no extension to tubes or ovaries. The pathologist reported choriocarcinoma of the uterus, with the cervix and ovaries showing no tumor.

Following discharge from the hospital, the patient felt well, gained weight, had very little cough and no hemoptysis, and hemoglobin remained satisfactory. About Jan. 15, 1957, she noticed a swelling in the left labia. Examination revealed a mass in the left labia in the region of Bartholin's gland which appeared to be a metastatic lesion. Pregnancy test was positive and hemoglobin was 15.6 Gm. The vaginal mass was excised and reported as metastatic choriocarcinoma of the vagina.

X-ray examination of the chest on January 30 revealed a remarkable change in that the multiple widespread metastatic deposits throughout both lungs had practically disappeared, so that her chest appeared almost normal (Fig. 5).

The patient again progressed quite well, but was readmitted to the hospital on Feb. 23, 1957, because of severe pain in the buttocks and down the left leg. X-ray pictures of her spine, pelvis, and hip joints failed to show any changes. Chest x-ray was normal. It was felt that she probably had involvement of the vertebrae and spinal cord nerve roots. Large amounts of narcotics were required to control her pain. On March 7, a lumbar subarachnoid injection was done using absolute alcohol. This gave moderately good relief from pain, and she was able to get along on only small amounts of opiates. Deep x-ray therapy was started over the lumbosacral spine.

On March 12 and 13, she showed remarkable improvement in that she had less pain, became ambulatory, and required only minimal amounts of narcotics.

Suddenly, on March 14, she developed headache, had a convulsion, and became comatose. She remained in deep coma. There was evidence of right flaccid hemiplegia. It was felt that she had multiple cerebral metastases with hemorrhage. On March 15, she had another hemorrhage and became less responsive. A lumbar puncture showed grossly bloody spinal fluid and she expired on March 16, 1957. Permission for an autopsy was not granted.

Fig. 4.

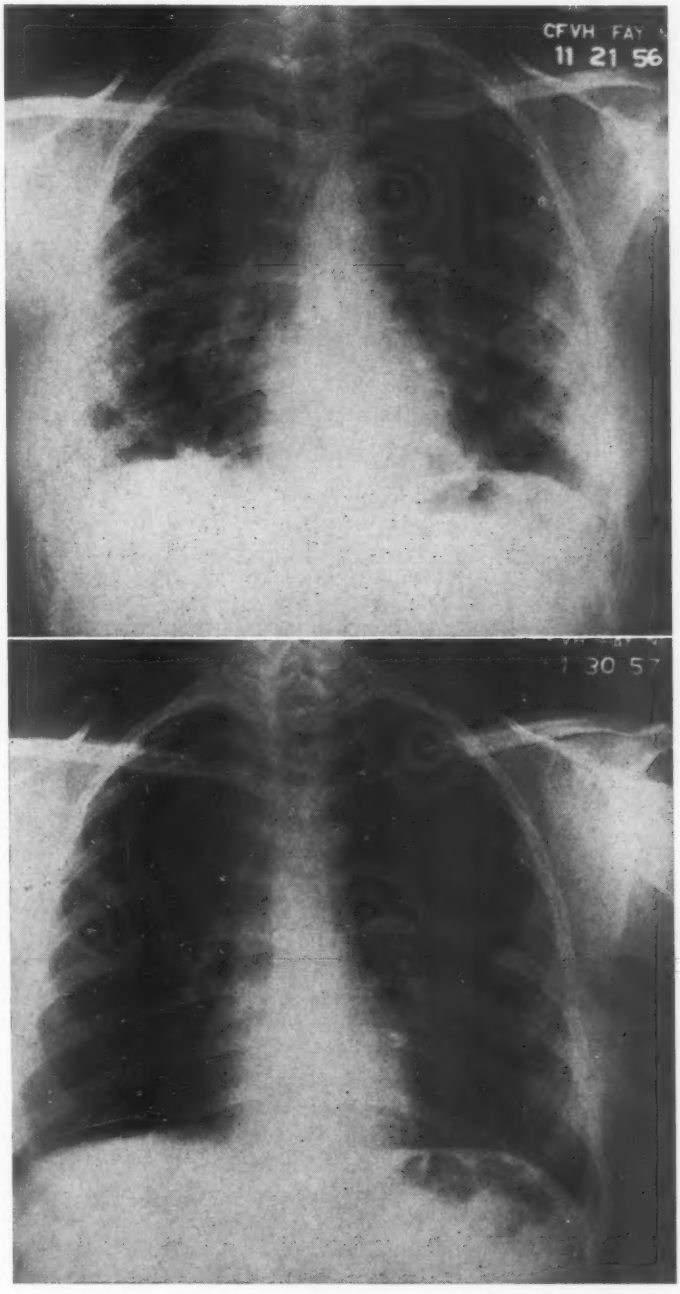

Fig. 5.

Fig. 4.—Nov. 21, 1956. Widespread multiple nodular densities throughout both lungs representing metastatic neoplastic disease.

Fig. 5.—Jan. 30, 1957. Remarkable change in that the multiple widespread metastatic deposits throughout both lungs have practically cleared.

Comment

This case of choriocarcinoma is characteristic in that it followed a mole and metastasized to lungs, vagina, and brain. It is unusual in that lung

metastases disappeared following removal of the uterus. The mechanism by which this happens is obscure. Hertig[14] suggests that it is probably related to the phenomenon of disappearance of trophoblast from the lungs and placental sites of normal postpartum patients. Possibly, the maternal tissues exhibit a defensive mechanism which holds the trophoblasts within normal limits[15] or perhaps a lytic substance destroys chorionic tissue.[16]

Summary

1. A case of choriocarcinoma with metastases to lungs, vagina, and brain is reported.

2. X-ray evidence is presented showing a regression of lung metastases following hysterectomy.

We are grateful to Dr. George Cameron, Pathologist, Cape Fear Valley Hospital, Fayetteville, N. C., for his pathological study and photography.

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PREGNANCY WITH DIABETES MELLITUS COMPLICATED BY HYDRAMNIOS AND LOSS OF FETAL MOVEMENTS*

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FEW cases have been reported of pregnancy in a diabetic patient, complicated by hydramnios associated with loss of fetal movements and good fetal heart tones. This is probably because no obstetrical service accumulates a large number of such cases. This is a report of 2 recently observed private cases. It is unique in that both cases were seen within 10 days of the same stage of pregnancy, and both patients were in the hospital at the same time.

Case Reports

CASE 1.—Mrs. E. L. R. (13806) was a 27-year-old primigravida who had had diabetes for 20 years, with onset at age 7. She had a moderate, and at times severe, diabetes, although this was not shown by eyeground changes, nor by x-ray findings of calcified pelvic vessels. The diabetes remained under good control throughout pregnancy except for one period of hospitalization, but the internist found it rather difficult to control the brittle character of her diabetes. The patient was placed on the Smiths' stilbestrol routine early in pregnancy. The estimated date of confinement was Jan. 10, 1957.

On Nov. 7, 1956, there was questionable hydramnios for the first time. On November 14 hydramnios was definitely present but not marked. On this date premature labor appeared to be starting and the patient was hospitalized at Charlotte Memorial Hospital. She was put on Lutrexin and the contractions stopped after 10 to 12 hours. She was discharged from the hospital after a week but Lutrexin was continued for a total of 11 days. On November 26 the patient said that she was not certain that any fetal movements had been felt for 48 hours. She was immediately readmitted to the hospital, whereupon the fetal heart tones were found to be normal. One wondered if the Lutrexin could be responsible for the lack of fetal motion, although it did not seem likely. Moderate hydramnios was present, representing a definite increase from that on November 14. X-ray examination (Fig. 1) showed a slight halo around the fetal head. A few hours after admission, the patient felt faint fetal movements, which continued for the next 3 days, with the fetal heart tones remaining good. The patient was 34 weeks pregnant. Repeat x-ray examination on the fifth day of decreased fetal motion showed that the halo had not increased. It was decided that immediate interruption of pregnancy was indicated. Accordingly, that same day (Nov. 29, 1956) a low-flap cesarean section was performed under spinal anesthesia, and a 5½ pound baby was delivered. The baby was markedly edematous, moderately hypertonic for 3 or 4 days, with rapid and shallow respirations but no serious respiratory difficulty, and he did well. The mother had an uneventful convalescence.

Comment.—In retrospect, the cesarean section should have been performed 3 days earlier when the first change in fetal movements was reported. To procrastinate in such a situation is to risk fetal disaster.

*Presented at the Twentieth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hollywood, Florida, Feb. 1 to 5, 1958.

CASE 2.—Mrs. K. H. (190168) was a 33-year-old gravida ii (one abortion at 5 months), para 0, who had had moderately severe diabetes for 5 years. Early in pregnancy this patient felt that, because of financial considerations, she could not remain a private patient and was referred to the clinic at Charlotte Memorial Hospital. She was hospitalized once on the ward service for control of the diabetes. She remained a clinic patient until Nov. 13, 1956, when she returned to the office and again became a private patient. The estimated date of confinement was Jan. 20, 1957. The patient was placed on the Smiths' stilbestrol routine but she did not take the medication.

On November 13 the diabetes was well controlled, but some hydramnios was already present. A strict toxemia regime, including Diamox, was instituted. The patient was seen again on Nov. 26 in the office and hospitalized immediately since she had gained 11 pounds during the 2 week interval and the hydramnios was marked. There was considerable edema of the lower extremities, the blood pressure was normal, and the urine showed a trace of albumin. X-ray examination showed a slight halo effect. At this time the patient was 32 weeks pregnant.

Fig. 1.—Case 1. X-ray showing slight fetal halo.

During the next 6 days the baby remained normally active and the fetal heart tones were normal. The blood pressure remained normal and the urine showed a trace of albumin. The patient lost several pounds of weight. Because of dyspnea, transabdominal amniotomy was done on two occasions, 800 c.c. being withdrawn the first time and 1300 c.c. the second time. At the time of the second amniotomy, on December 2, slightly blood-tinged fluid was obtained. A few hours after this tap the patient stated that the baby definitely stopped moving, although the fetal heart tones remained normal. This patient had also been on Lutrexin and again we wondered if this could possibly play any part in the lack of fetal motion, as in the first case. The next day the baby was not moving but the fetal heart tones were still normal. Immediate termination of the pregnancy by cesarean section was considered, but it was finally decided to postpone the operation for another day or so, playing for additional time, since the patient was only 33 weeks pregnant and it was not felt that the baby was as large as in the first case. It must be admitted that the fact that the first patient had felt decreased-to-absent fetal movements for 5 days with fetal heart tones still good gave us a false sense of security! We failed to allow the proper consideration for the severity of the hydramnios and the length of time the hydramnios had been present. When a repeat x-ray examination (Fig. 2) on the morning of December 3 showed a marked halo in comparison with the one taken on November 26, full significance was not given to this finding. During

the night of December 3, the fetal heart could not be definitely heard. The next day it was thought that it could be heard faintly on several occasions, and finally, a cesarean section was performed, with delivery of a macerated, markedly edematous, stillborn infant weighing 6 pounds, ½ ounce. No sign of trauma to the baby as a result of the paracentesis could be found. Autopsy revealed no other abnormalities. Post partum, the patient had several days of morbidity but made a good recovery.

Comment.—Obviously the "desperation" cesarean section was a mistake. It should at least have been performed immediately after the patient first noticed absence of fetal movements while the fetal heart tones were still normal. In retrospect, however, good obstetrical judgment would have dictated that the patient be hospitalized at the first suggestion of hydramnios (30 weeks), and that the pregnancy be interrupted at 32 weeks in view of the marked hydramnios, in spite of the risk of prematurity. One can only speculate about the outcome, but interruption would seemingly have given the baby a better chance of survival.

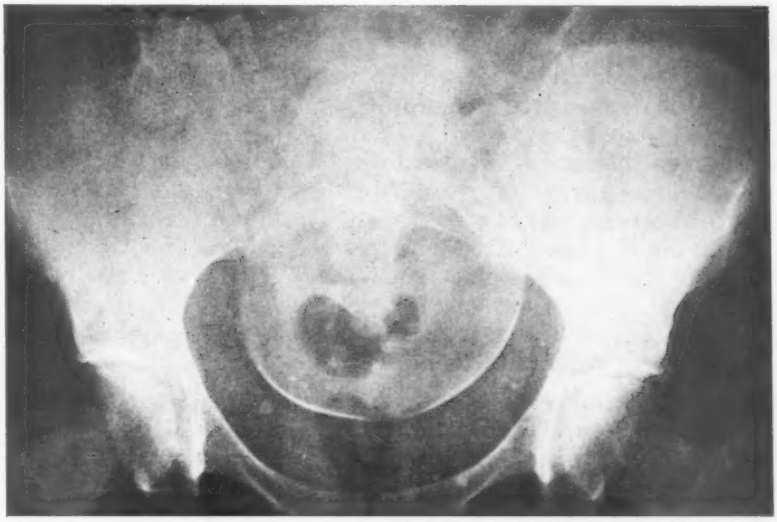

Fig. 2.—Case 2. X-ray showing marked fetal halo.

Comment

It is well known that hydraminos may occur as a complication of pregnancy in the diabetic patient and no one seems to have been very successful in preventing it. In the literature of recent years the frequent association of hydramnios with intrauterine fetal death has been stressed. Very little has been written, however, about the loss of, or decrease in, fetal movements while the fetal heart tones remain normal. This should be considered a sign of impending fetal death and needs to be stressed further.

Carrington[1] of the Temple University Hospital feels that a decrease in fetal movements is a grave prognostic sign. She states that these patients must be delivered by cesarean section when the cervix is not ripe. It must be borne in mind that these babies have a higher incidence of hyaline membrane disease than do infants of nondiabetic mothers delivered by cesarean section, particularly when they are already sick and edematous in utero. Carrington points out that the halo sign on x-ray is a late sign and by the time there is enough edema to be visible over the scalp the baby is already very sick. She outlines the following routine: (1) Hospitalize with the first evidence of significant fluid retention or abnormal increase in the height of the fundus, since so little is known about the formation, let alone the reversal, of amniotic fluid collection; perhaps

2 or 3 weeks may be gained in a reasonable number of cases if all other factors are controlled. (2) Order bed rest with bathroom privileges, increase the protein in the diet, restrict salt, prescribe Diamox, check blood pressure, weight, 24 hour urine proteins and fetal heart tones daily. (3) Avoid amniotomy except in the *rare* and acute form which impairs circulation and respirations. (4) Deliver the patient with the least manipulation possible after 33 weeks if hydramnios increases; if a reliable patient notices reduced fetal movements; if edema, proteinuria, or hypertension develops or increases despite treatment.

Given[2] of the New York Hospital stated in 1952 that hydramnios is considered the most significant antepartum complication because of its associated high fetal mortality.

Tolstoi, Given, and Douglas[3] stated in 1953 that, in considering delivery, one must weigh the dangers of prematurity against those of intrauterine death. Each case must be evaluated individually. After the thirty fourth week there is little gained by waiting, and a chance for a viable infant may be lost by delay.

Given and Tolstoi,[4] however, in April, 1957, expressed disappointment in the failure of today's accepted principles of treatment to reduce fetal mortality. They have found that if the patient's condition deteriorates so badly around the thirty second week that one is obliged to terminate pregnancy in an effort to get a live baby, the baby rarely survives. Recently they have been trying to carry the patient to 35 weeks, even in the face of significant amounts of hydramnios or elevation in blood pressure. They feel that there is some unknown factor which makes for good babies or for bad babies. The same authors further state that Lars Hagbard, with extensive personal experience and after a very comprehensive review of the world literature, reached the same conclusion that delivery before the thirty fifth week is highly dangerous to the baby.

Priscilla White[5] said that a decision for emergency delivery should be made if the patient has (1) pre-eclampsia, (2) hydramnios, (3) a fall in pregnandiol excretion, (4) fetal halo, or (5) if the mother reports loss of fetal motion when the fetal heart tones are good.

Jones[6] of the Providence Lying-In Hospital said in 1953 that prompt delivery before the condition progresses from simple diabetic edema to frank hydrops may effect a salvage.

Peel[7] of Kings College Hospital in London stated that the exact and immediate cause of intrauterine death in hydramnios has not yet been determined but presumably it indicates failing placental function. Furthermore, he feels that transabdominal amniotomy is apt to cause intrauterine fetal death within a few days. White, Gillespie, and Sexton,[8] as well as Carrington,[1] advocate this procedure, however, when necessary.

Interestingly enough, White and associates[8] describe a case exhaustively reported by Bennewitz in 1824 of a patient whose symptoms of diabetes became intensified in her fifth pregnancy. This pregnancy was complicated by hydramnios. No fetal motion was noted for one month before delivery. During the delivery the baby was alive but great difficulty was encountered when the shoulders became stuck, and finally a 12 pound stillborn infant was delivered.

Conclusion

These two cases again demonstrate the danger to fetal survival when hydramnios occurs as a complication of pregnancy in the diabetic patient. The loss of, or decrease in, fetal movements while the fetal heart tones remain normal

is a grave sign, usually implying impending fetal death. When hydramnios is present, the pregnancy should be interrupted before this complication arises if the stage of pregnancy makes it at all feasible.

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TERM ABDOMINAL PREGNANCY WITH SURVIVAL OF MOTHER AND INFANT*

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ABDOMINAL pregnancy is a condition well known but seen with great rarity. It is even more unusual when such a pregnancy progresses to term with the delivery of a normal living infant and an uncomplicated postpartum course for the mother. Few individuals have the good fortune to observe even a handful of such cases. Charlewood[1] and King[2] are notable exceptions, having had the opportunity to observe 52 and 12 cases, respectively. In King's experience, these 12 cases were seen over a period of 21 years during which over 60,000 normal full-term deliveries occurred. Therefore, careful observation of each such case and its reporting in the literature are not only justified but perhaps advisable. In presenting the following case, it is hoped that total knowledge will be advanced.

The patient was a 34-year-old Negro multigravida, who was first seen in the City Prenatal Clinic between the eighteenth and twentieth weeks of her pregnancy. At this time, her weight, blood pressure, and urine were found to be normal. She complained of right lower quadrant pain together with some nausea and vomiting of 24 hours' duration. Examination revealed what seemed to be enlargement of the uterus consistent with a 4 months' pregnancy. The uterus was thought to be somewhat more firm than average and for this reason a "fibroid" was considered. No adnexal abnormality was palpated. The pelvis was considered adequate for normal delivery. Because of the right lower quadrant pain and spasm, the patient was referred to a surgeon for evaluation of possible appendicitis. She was hospitalized for a period of 2 or 3 days, during which time the symptoms regressed and she was discharged without operation. She was then followed in the Prenatal Clinic for a total of seven subsequent visits, during which time the weight gain and blood presure remained within normal limits. On May 6, 1952, at a routine prenatal visit, 5 weeks before term, she complained that she had been sick at home for several days with general abdominal discomfort, nausea, and vomiting. She was admitted to the labor room on June 15, 1952, apparently at term and in spontaneous labor. The fetal heart tones were good. On admission examination, it was evident that there was a transverse presentation and that the cervix was not dilated.

X-ray examination was ordered and completed with the following report: "A single fetus lying transverse with the spine superior and with a foot presenting. The vertex is in the right upper quadrant and the entire fetus is quite high. The uterus cannot be outlined. An additional view was made and the uterine wall cannot be identified and a contracted uterus cannot be visualized in the pelvis. The placenta has not been located. The most interesting finding is that of intestinal gas between the fetus and the abdominal wall.

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"Conclusion: A transverse presentation with findings to indicate an extrauterine pregnancy. The fetus is near maturity."

With this evidence at hand, a laparotomy was decided upon with the provisional diagnosis of an extrauterine pregnancy. With the patient under general anesthesia, a lower midline incision was made. Externally the peritoneum appeared muddy and thick. A large amount of cloudy, straw-colored fluid was found in the peritoneal cavity. The anterior abdominal wall was free of adhesions and the fetus was found lying beneath the greatly thickened omentum. A foot could be seen protruding into the abdominal cavity through an opening in the amniotic sac immediately above the symphysis. This opening was enlarged and a living male infant was removed by breech extraction. Inspection revealed that the pregnancy was entirely extrauterine. The placenta filled the pelvis and was attached to the right lateral and posterior walls of the pelvis. The amniotic sac displaced the abdominal contents upward and the thickened omentum was adherent to its anterior surface. The uterus was enlarged approximately twice normal size. The right tube and ovary could not be visualized. The left adnexa appeared normal. The cord was ligated and cut near its placental attachment, the placenta was left in situ, and the abdominal wall was closed in layers without drainage. The patient's postoperative course was benign. She had very few complaints and was ambulatory on the third day, at which time prophylactic antibiotics were discontinued.

The infant appeared to be entirely normal without evidence of injury or abnormality. He had a normal neonatal course, was breast fed with supplementary bottle feedings, and was discharged with his mother.

The patient was seen for a period of 6 months following the operation during which time the pelvic mass, which was readily felt in the location of the placenta, appeared to regress slowly and the patient had no unusual complaints. She then moved to Washington, D. C., where she was admitted to a hospital with complaints of generalized lower abdominal cramping pain. It is reported that a laparotomy was contemplated for removal of the remaining placental tissue but this was canceled when the patient's complaints subsided spontaneously. She was seen again by us 2 years after operation. At this time, she was admitted for generalized cramping abdominal pain of 4 days' duration.

This illness appeared to be a simple gastroenteritis but opportunity was taken for examination with the following significant findings: The uterus was anterior and normal in size, and the mass, which had previously been noted on the right of the pelvis, appeared to be completely resolved. X-ray examination and barium enema revealed a low-density calcification in the right side of the pelvis which did not appear in any way to effect immobilization of the cecum or to interfere with the flow of the bowel content.

The infant at this time was progressing in a perfectly normal manner.

The prenatal history in this case is quite typical. In retrospect, there was evidence of abnormality when the patient was first seen and at one subsequent prenatal visit. Preliminary examination in the labor room established the fact of pregnancy and of an abnormally high and transverse presentation. As the patient was not in undue distress, great significance was given to the noting of intestinal gas shadows anterior to the fetus. Where a diagnosis of intestinal obstruction is entertained, this finding might, of course, be invalidated. In a review of a number of reported cases, it is evident that intestinal obstruction is considered frequently during the prenatal course of patients with abdominal pregnancy. It does not appear, however, that this is a frequent impression at the time the patient is admitted at or near term when labor readily explains the discomfort which is present. The absence of a uterine shadow was also noted. It has been suggested by Cross, Lester, and McCain[3] that the finding of intestinal gas shadows anterior to the fetus be added to the x-ray findings suggestive of abdominal pregnancy.

The management of the placenta has provoked considerable discussion. It appears conclusive, however, that conservative management is to be followed because of the danger of uncontrollable bleeding. Millen[4] quoted a personal communication from Ferris of New Orleans, indicating that in only 2 instances among 39 abdominal pregnancies seen was secondary removal of the placenta necessary. Others have reported similar experience, and in this instance it is obvious that the placental mass slowly regressed in size, eventually becoming at least partially calcified and producing no symptoms.

Conclusion

A case of a full-term intra-abdominal pregnancy is presented wherein a living child was obtained and the mother suffered no morbidity.

The suggestion is made that the finding of intestinal gas shadows anterior to the outline of the fetus be given significance in the differential diagnosis.

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Gynecology

THE STEIN-LEVENTHAL SYNDROME*

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ONE of the most dramatic and satisfying experiences in the practice of gynecology is the establishment of true menstruation and fecundity following a simple wedge resection in certain patients with amenorrhea and bilateral polycystic ovaries. How these cysts occur, why they produce a definite symptomatology, and why the wedge resection leads to a re-establishment of normal physiology has led to much speculation and some experimentation. In the light of our present knowledge, there are certain facts that are well established, but further investigation will be required to clarify the entire problem.

Grossly and on section, the mature ovary is normally a "cystic" structure. Of the numerous follicles found in the preadolescent ovary, only a small number eventually go through the complete cycle including ovulation and corpus luteum formation. The vast majority fall by the wayside by a process known as atresia folliculi. In the cystic stage of atresia, the follicle may be lined by granulosa cells or there may be no granulosa at all, the wall being formed by the theca interna layer. Normal ovaries are the seat of such microcystic degeneration with the cysts eventually becoming obliterated by cicatrix. Under certain pathologic conditions, numerous follicles may mature to the cystic stage and fail to go on to cicatrization. When the change progresses without ovulation and produces enlargement of the ovary with markedly thickened tunica albuginea and hyperplasia of the theca interna cells, an anatomic entity presents itself which has been labeled bilateral polycystic ovaries. Such ovaries may attain an enlargement which remains static for years. When these anatomic findings are associated with menstrual irregularities ending in amenorrhea or oligomenorrhea, sterility, and hirsutism, a clinical entity or syndrome presents itself which was described by Stein and Leventhal in 1935.[1]

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Symptoms and Findings

The syndrome is characterized by *secondary amenorrhea, sterility, bilateral polycystic ovaries,* and *hirsutism,* occurring in young women in the second or third decade of life. In our earlier cases, obesity was commonly present, but a review of larger numbers has shown no greater incidence than expected in normal individuals. The menstrual history is variable and depends upon the duration of the disturbed physiologic state and the changes in the ovary. The secondary amenorrhea may be preceded by normal menarchal and adolescent periods. Irregularity then occurs (or may be present from the beginning) which is characterized by lengthening intervals interrupted by scanty flows. On occasion, there may be frequent bleeding or even menorrhagia, as was noted by Ingersoll[2] in 5 of 37 cases and by Stein in 8 per cent of his cases. The final amenorrhea may be interrupted by occasional bleeding a few times yearly, or may be an absolute phenomenon lasting for years. Persistent anovulation characterizes all patterns of bleeding in these cases. The basal body temperatures show a continually monophasic curve, the vaginal smears demonstrate an estrogenic effect, and the endometrial biopsies reveal a low proliferative endometrium. In the early states, there may be a reversal of the disorder; ovulation may break through and be followed by pregnancy. In the few cases where this occurred in our series, menstruation was normally re-established following pregnancy.

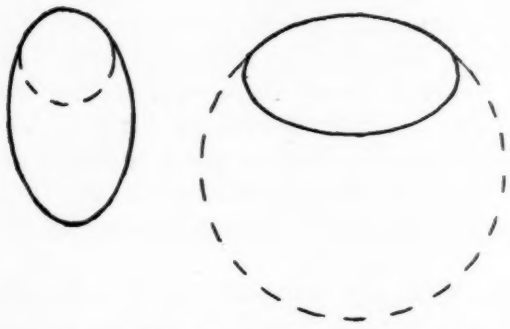


Fig. 1.—Dotted lines indicate "mind's-eye" distortion of size when only one segment of the ovary is palpated.

Pregnancies also occurred before the onset of the syndrome, although rarely. In one patient there was recurrence of the syndrome following a pregnancy which had been made possible by wedge resection. In the end stages, the disease becomes static and irreversible by all presently known therapies except wedge resection. The length of time these patients go without menstruating is remarkable. Stein and Leventhal[3] have previously reported on 2 patients with amenorrhea of 7 and 8 years' duration, respectively. Both patients responded to wedge resection with prompt establishment of monthly ovulatory bleeding and pregnancy occurred without further work-up. Bergman[4] reported upon a patient with amenorrhea of 10 years' duration who responded to wedge resection with return of normal menstruation followed by pregnancy.

The demonstration of bilateral polycystic ovaries is the keystone in the diagnosis. It is sometimes difficult to detect these ovaries on routine bimanual examination, and, as a matter of fact, they can be definitely felt in only about one half of the women who harbor them. Obesity, marked pelvic inclination, abdominal rigidity, and inaccessibility of the ovaries to the palpating fingers are factors accounting for the difficulty of being absolutely sure

of the size and contour of the ovaries. If the palpating fingers outline only a segment of the ovarian surface, the actual size of the mass may be distorted by the "mind's eye" (Fig. 1). When the examiner is not absolutely sure, more accurate and objective methods of diagnosis should be used. These include pelvic roentgenography and culdoscopy. Examination under anesthesia may be done. At the Michael Reese Hospital, pneumoroentgenography and culdoscopy are used very often in patients with doubtful pelvic findings. We have been rewarded and at times surprised by discovering pathologic conditions missed on bimanual examination. With these additional diagnostic methods, exploratory laparotomy should rarely be needed.

The sudden appearance of male type hirsutism is significant and occurs in approximately 50 per cent of the patients. When present, it may be very mild, involving the face, upper lip, arms, legs, and lower abdomen; sometimes it may be very extensive. Rarely, it may be associated with mild forms of virilism, such as enlarged clitoris, atrophied breasts, etc. This type of hirsutism (ovarian) is most often associated with normal urinary excretion values for the 17-ketosteroids.

Fig. 2.—Typical "oysterlike" polycystic ovaries noted at operation. Each ovary is larger than the corpus of the uterus.

Incidence

The incidence of the typical syndrome is very low. The gynecologist should be cautious in making a diagnosis and reluctant to propose surgery in the absence of very definite symptoms and findings. If other causes for amenorrhea are not ruled out, the operation will be marked by failure. Vara and Niemineva,[5] in a review of 9,000 gynecologic laparotomies, found 6 cases of the Stein-Leventhal syndrome. Since the majority of patients present themselves with a complaint of infertility, most statistics of incidence come from this group. Johansson,[6] in a study of 370 thoroughly evaluated wives who complained of infertility, found 5, or 1.45 per cent, with the syndrome. Cohen[7] performed culdoscopy on 316 patients complaining of infertility, and found polycystic ovaries in 9, or 2.8 per cent. Since Stein's first performance of wedge resection in 1929 to date (29 years) he has studied 96 women on whom he performed wedge resection. Leventhal and Cohen[8] in 1951 reported

an analysis of 10 cases from the Michael Reese Hospital covering a 4 year span (1945-1948). Since 1948, I have personally studied and documented an additional 8 cases of the syndrome which responded to wedge resection. Even though some additional cases may have misesd our attention, the sparsity of the number of cases at the Michael Reese Hospital (114 in 29 years) again emphasizes the infrequency of the bilateral polycystic ovaries of the Stein-Leventhal syndrome. Enlarged ovaries per se are not a sufficient indication for laparotomy.

Pathology

At operation, the ovaries are enlarged grossly to a size approaching and at times exceeding the size of the uterine corpus. The enlargement is in the form of an interpolar elongation, the ovary appearing tense and oval or "egg shaped." The tunica is thick, tough, and pearly white. There is usually no bulging of individual cysts on the free surface. Cut sections reveal a thick, fibrous capsule surrounding a stroma containing innumerable follicle cysts

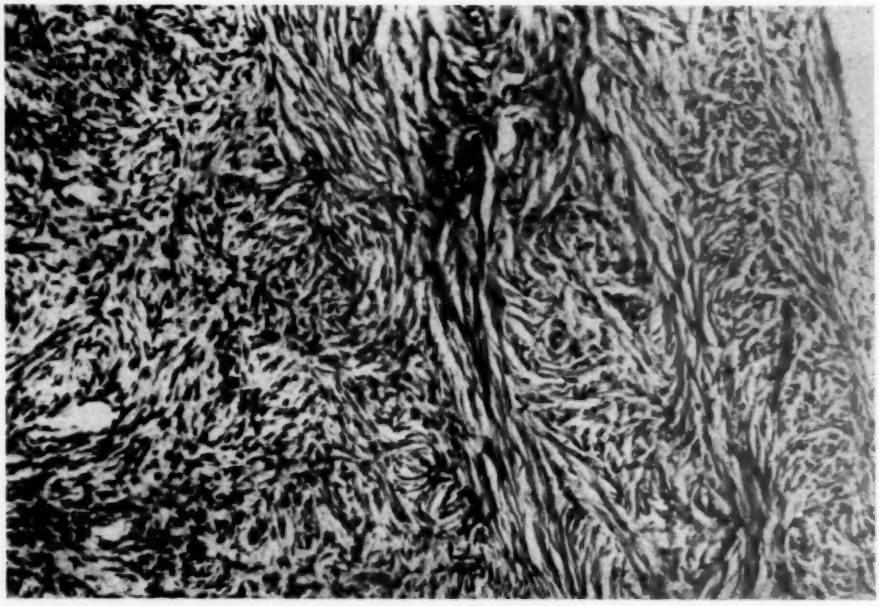
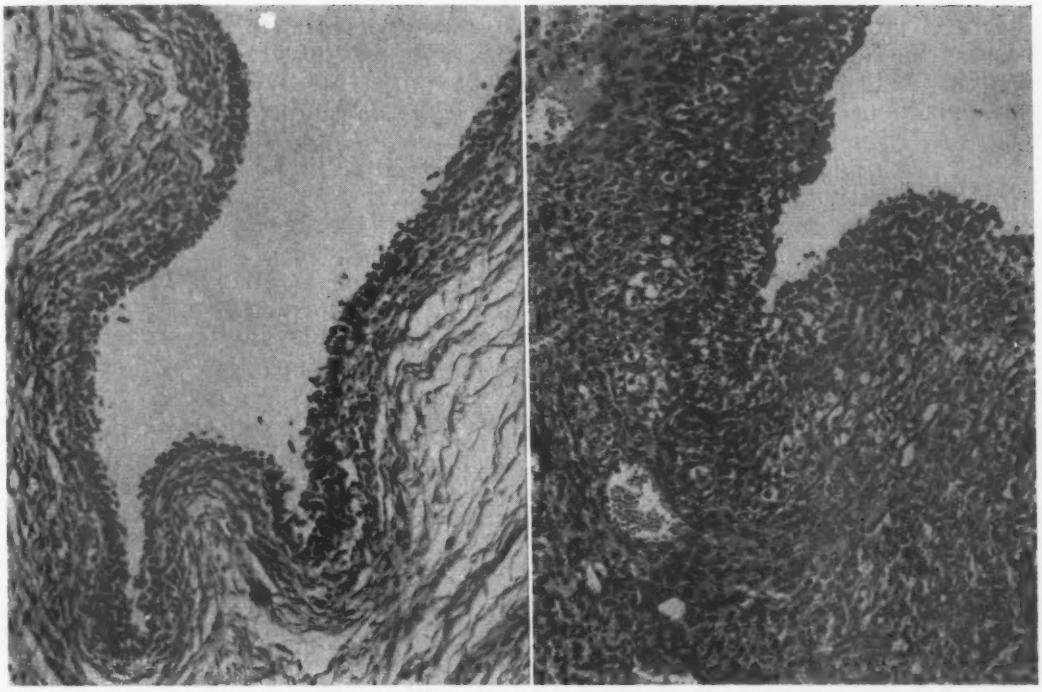


Fig. 3.—High power of section showing the characteristic thickening and fibrosis of the tunica albuginea.

filled with clear fluid. There is sharp demarcation between the capsule and underlying stroma. The cysts appear to be "pushed down" towards the hilus of the ovary by the thick fibrous tunica. The follicles may or may not have layers of granulosa cells. One of the most significant and consistent findings is a hyperplasia of the theca interna cells, which most frequently show evidence of luteinization. In some sections, there is proliferation of the theca surrounding corpora albicantia, indicating that something interfered with the regression of the theca cells. The hyperplasia is marked by numerous mitotic figures and hyperchromatism and is very richly vascularized. The impression one gets from noting these changes is that either something has stimulated the theca cells, something is missing which under normal conditions inhibits the growth of the theca cells, or there is a primary independent growth of the theca cells. The sections are characteristically marked by the absence of corpora lutea or corpus luteum cysts.



A. *B.*

Fig. 4.—*A*, Section of cyst lining from a normal follicle, showing relatively thin layer of theca compared to *B*, the lining of a cyst in the Stein-Leventhal ovary showing marked activity of the theca (hyperplasia and luteinization).

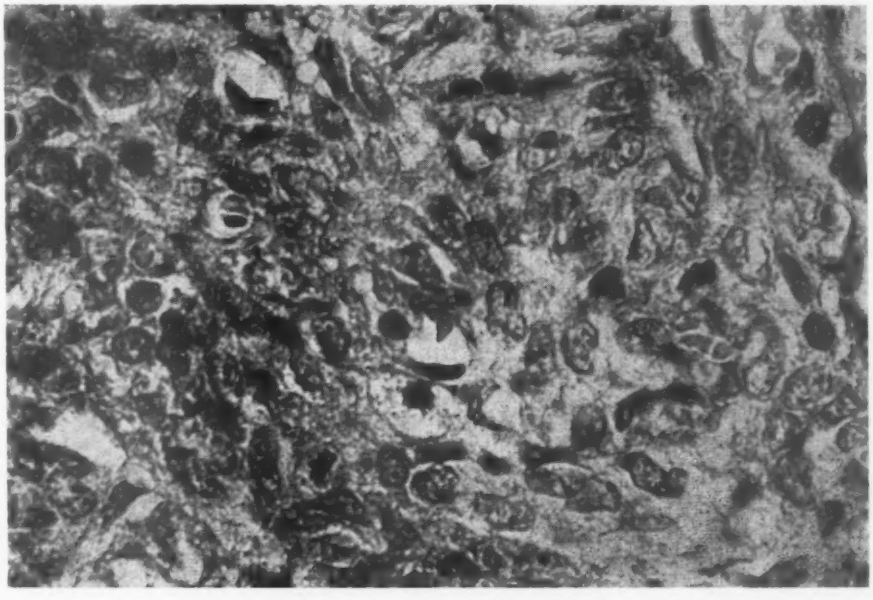


Fig. 5.—A high power of a section of Fig. 4, *B*, illustrating marked hyperplasia with many mitotic figures.

The endometrium in the vast majority of cases reveals a proliferative picture, mildly stimulated. In a few cases hyperplasia is found. In other cases, the endometrium is atrophic and, in a few, secretory changes are noted. When a secretory endometrium is found, the ovaries show marked luteinization of the theca, but no evidence of ovulation or corpus luteum formation (Figs. 2 to 5).

The paradox of a wide range of endometrial reactions with ovarian hyperthecal activity may be explained by changes in the estrogen-androgen balance. This is understandable when it is noted that theca-cell tumors may be associated with the secretion of estrogen, producing enlargement of the uterus with proliferative endometrium; the secretion of androgenic steroids, producing masculinization and atrophic endometrium; or, progestins with secretory endometrium. Androgens may also cause a proliferation of the endometrium, as do the estrogens.

Pathogenesis

Since both ovaries are equally affected, it appears likely that the original stimulus comes from outside the ovary. Once the ovarian changes occur, the gonads may act independently of such influences. Certainly the removal of the ovarian changes (e.g., thickened tunica and hyperplastic theca) restores the woman to a normal physiologic state. It is possible that removal of the "block" in the ovary may re-establish homeostasis by producing normal "kickbacks" to the hypophysis. Studies have been made of the pituitary, adrenal, and thyroid glands in patients exhibiting the syndrome in an attempt to determine whether the extragenital endocrine glands, whose functions are closely bound up with those of the ovary, are responsible for or are associated with the ovarian changes.

Anterior Pituitary Gland.—The present evidence involving this gland is confusing and controversial. Since the gonadotrophic hormones cannot be identified presently by chemical-physical methods, their action must be determined by bioassay, a method open to varied interpretation by different investigators. The luteotrophic hormone (LTH) can be ruled out as a causative factor since the polycystic ovaries contain no corpora lutea. Observations on the production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) separately or in combination have been studied. Some observers believe that the changes are due to hypersecretion of FSH. Some have shown no increase, and others a decreased secretion. There are those who state that the changes are due to a prolonged low-grade secretion of LH. Since a completely satisfactory method of testing for LH is not presently available, it is difficult to prove such a contention. The fact that the ovaries are characterized by luteinization of the theca in most cases, however, lends support to this proposal. The production of numerous unruptured follicles by the injection of anterior pituitary extracts into experimental animals has been demonstrated repeatedly. In the woman, the administration of similar extracts can cause amenorrhea with polycystic changes in the ovaries. These extracts contain a combination of FSH and LH and the ovaries return to normal when the stimulus is removed. No investigator thus far has produced the typical permanent refractory polycystic ovaries by the administration of anterior pituitary extracts.

Sommers and Wadman,[9] in a study of the pathogenesis of polycystic ovaries, stated that the change is due to hypersecretion of FSH. They collected 24 instances of bilateral polycystic change in examining the ovaries from unselected adult women at autopsy. One half of the women had clinical symptoms of the Stein-Leventhal syndrome. Examination of 7 pituitary

glands from this group showed a marked increase in the numbers of normal heavily granulated basophils which were collected into hyperplastic nodules. These are the cells which produce FSH as well as ACTH. The authors stated, "these patients had a form of endogenous Aschheim-Zondek or Friedman test reaction to their own excessive gonadotropins." In a few cases where we have had occasion to do A-Z tests on patients with the syndrome, the results were negative. This, however, does not exclude the possibility of prolonged minimal secretion insufficient to stimulate the ovary of the test animal.

Many authors have been unable to demonstrate an increase in the urinary excretion of FSH.[10-14] Here, again, the evidence does not preclude a prolonged increased production with a qualitative rather than a quantitatively measurable result. In the Massachusetts General Hospital series of 37 cases of the Stein-Leventhal syndrome, Ingersoll[2] reported investigations of the urinary excretion of FSH in 26 patients. Twenty-two had normal levels, 1 had a lower level, and 3 a slightly elevated level. The finding of a moderately elevated level was not significant since such levels may be found in normal women. He asserted that the method of assay he used is one that possibly measures both FSH and LH. Ingersoll and McDermott[13] were unable to test for luteinizing hormone (LH) but advanced the suggestion that the ovarian changes were due to an excess of LH. Bergman[4] reported 5 typical cases successfully treated by wedge resection. In all of them, the excretion of gonadotrophic substances was normal. There was a slight increase of the 17-ketosteroids in 3 of the patients, only 1 of whom manifested hirsutism. In 3 of the patients on whom postoperative hormone studies were done, no change over the preoperative values was noted.

Keettel, Bradbury, and Stoddard[15] demonstrated a deficiency of FSH production and an increase in LH in patients with typical polycystic ovaries. They described a biological test for LH based on evidence that LH acts primarily on the theca cells while FSH acts primarily on the granulosa cells. They injected gonadotrophin extracts from 24 hour urine specimens into immature rats and studied the ovaries histologically. If the theca cells were stimulated to hypertrophy with little stimulation of the granulosa, the extract was considered primarily LH in character. If the reverse were true, with the formation of many cystic follicles, the extract was considered to be primarily FSH. Using these criteria, the authors demonstrated an excess of LH in 10 of 11 patients whom they considered to have the Stein-Leventhal syndrome. They also found that injections of FSH caused enlargement of the ovaries in 12 of 13 patients with the syndrome (caused by enlargement of the cystic follicles) while in a control group, only one of 36 patients showed a similar response. The enlargements regressed after 2 weeks. They stated that "the fact that polycystic ovaries respond so readily to FSH indicates that many of the follicles are in a state of stasis rather than one of cystic degeneration or atresia. The response of these static follicles to FSH could be interpreted as proof of a deficiency of FSH." From their experiments they proposed that the urinary assay of LH and the response of the suspected ovaries to FSH injections are diagnostic aids in the recognition of the Stein-Leventhal syndrome, especially in the early atypical cases showing lesser degrees of ovarian enlargement.

In summary, the role of FSH in the production of the Stein-Leventhal syndrome is not clarified but evidence points to the excessive secretion of LH as a causative factor.

Adrenal Gland.—The close relationship of adrenal and ovarian function in hormonal homeostasis is well established. This is understandable from the

fact that both gonadotrophic and corticotrophic hormones are produced from the same cells in the hypophysis. Abnormal hyperfunctional states of the adrenal cortex as the adrenogenital syndrome and Cushing's syndrome may be associated with amenorrhea and polycystic ovaries. The administration of proper dosages of cortical hormones will inhibit ACTH production and enhance gonadotrophin secretion. This fact is utilized in the so-called "cortisone test" which will be discussed later in ruling out adrenal hyperplasia as a cause of ovarian dysfunction. Conversely, the ovary may affect the adrenal. In certain dosages, estrogens, by inhibiting FSH, may stimulate ACTH production and thus increase adrenocortical activity. This is noted physiologically in pregnancy.

Hirsutism occurred in approximately 50 per cent of our cases. Since it is a stigma of masculinization or defeminization, it aroused interest as to the possible abnormal production of an androgenic hormone in the ovary or adrenal, or both. Excessive androgens produced in the adrenal cortex are reflected in the urine by an increased excretion of 17-ketosteroids. Since the 17-ketosteroids are normal in the Stein-Leventhal syndrome, even though androgenic effects are present, it is assumed that the adrenal gland is not involved in the symptomatology. It is possible, however, that a minimal continuous estrogen secretion by the polycystic ovaries may produce some hyperplasia of the adrenal cortex. This contention may be proved or disproved if adrenal cortical biopsies are taken at the time of wedge resection, especially in patients who demonstrate masculinization. Evidence of such a relationship was shown by a case report of hyperthecosis of the ovary associated with hyperplasia of the reticular zone (androgenic) of the adrenal cortex, histologically proved.[16] This association may account for the few cases of the Stein-Leventhal syndrome with slightly elevated 17-ketosteroids and pregnane complex and has led some observers to believe that both organs may, at times, be involved in the symptomatology.

In summary, it is possible that the adrenal gland plays no role in the pathogenesis of the polycystic ovary syndrome, but may become secondarily involved. Most often, when a patient has amenorrhea and bilateral enlargement of the ovaries and the excretion of the 17-ketosteroids is elevated, the evidence points to adrenal disease.

Thyroid Gland.—There is no evidence that thyroid dysfunction may be a factor in the production of the syndrome. In the vast majority of our patients, the basal metabolic rate was normal. Buxton and Vande Wiele[17] made cholesterol determinations and radioactive iodine uptake studies on 6 patients and found them normal. Adequate thyroid therapy used empirically in a number of patients was unsuccessful in restoring normal menstruation. This held for patients in whom the basal metabolic rate was significantly low.

The Ovary.—The hyperplastic theca in the typical polycystic ovary may be compared to hyperplastic states in other glands of internal secretion. The stimulated theca cell contains the steroids which may produce estrogenic or androgenic effects. In numerous case reports of the syndrome, estrogen values were usually within normal range, but with little cyclic variation. Bergman[4] found normal excretion values, with no significant change postoperatively. Haas and Riley[14] reported upon 7 patients on whom bilateral wedge resection was done. Six responded successfully. FSH and estrogen values determined weekly preoperatively were within normal range. Ovulation was absent in all except one, in whom it was inconstant. Since the endometrium in most cases shows an estrogenic effect, it is possible that a mild prolonged secretion of estrogen may take place without reflecting itself in a measurable excretion

in the urine by present methods. Whereas it is known that large doses of estrogen will inhibit gonadotrophin production, it is believed that small doses may depress FSH while stimulating LH production.[18]

The cyclic administration of estrogens and progesterone has no effect on the ovarian pathology in the Stein-Leventhal syndrome. These hormones will stimulate the uterus, causing anovulatory withdrawal bleeding. The androgenic effect from the polycystic ovary is manifested by the appearance of hirsutism, and, on occasion, mild forms of virilism, in patients previously free of such findings. It is well known that steroids produced in the hyperplastic luteinized theca have the capacity, perhaps through the mediation of enzyme systems, of producing androgenic effects. This has been demonstrated in experimental animals and in women.[19-22] A close relationship between thecal hyperplasia and masculinization was shown by Culiner and Shippel.[23] Shippel[24] analyzed 37 cases of what he described as the hyperthecosis syndrome and found normal or at most only slightly elevated 17-ketosteroid levels, notwithstanding very marked masculinization in some cases. He stated that the theca-cell androgen, whatever it is, does not break down as a rule into a 17-ketosteroid as does the adrenal androgen. It is probable that a progesterone-like molecule, through change, becomes androgenic. In 2 of our patients who showed the most marked degree of hirsutism (1 bordering on virilism), pregnanediol excretions were consistently elevated, and the ovaries showed unusually marked degrees of hyperplasia and luteinization. It is also interesting to note that androgenic effects are produced by some ovarian tumors without an increased excretion of the 17-ketosteroids. Talbot and Butler[25] noted normal 17-ketosteroid levels in masculinizing arrhenoblastomas and contrasted these with very high levels in masculinization due to adrenal hyperplasia and tumor, thus inferring a different type of androgen from the ovary. Segaloff[26] reported a hilus-cell tumor of the ovary with true virilism (enlarged clitoris, receding hairline, hirsutism, change in voice, etc.) without significant increase of the 17-ketosteroids.

In summary, the steroids produced by the hyperplastic theca cells in the Stein-Leventhal ovary may produce an estrogenic effect or an androgenic effect, or a combination of both. The end organ effect is estrogenic in the majority of the patients. This is evidenced by hypertrophic changes in the endometrium. There is ample evidence that the theca, under certain conditions, can produce steroids with androgenic effect. Although the total 17-ketosteroids are not elevated, a greater percentage of the component 17-ketosteroids may be androgenic than is normally found. Therefore, when a patient with bilateral polycystic ovaries, amenorrhea, and hirsutism has a normal urinary 17-ketosteroid excretion, the evidence points to an ovarian lesion, but still does not exclude adrenal pathology.

Differential Diagnosis

A diagnosis of the Stein-Leventhal syndrome, with assurance that wedge resection will be successful, is made only after other causes of amenorrhea, polycystic ovaries, and hirsutism are ruled out. Diagnosis is facilitated by a detailed history, physical examination, gynecography, and/or culdoscopy for visualization of the ovaries, x-rays for enlargement of the pituitary or adrenal, and a determination of the urinary excretions of 17-ketosteroids and the "pregnane complex." Hyperplasia and new growths involving the ovary, pituitary, and adrenal glands must be differentiated because they may produce one or more of the triad of symptoms.

Considering the ovary, there is a large group of young patients with dysfunctional anovulatory bleeding and infertility associated with enlarged

ovaries due to follicle cysts and with endometrial hyperplasia. This type of dysfunction not infrequently responds to cyclic therapy or curettage. Any response to wedge resection in these patients is incidental and the dysfunction may recur at a later date. Masculinizing tumors of the ovary producing amenorrhea include arrhenoblastoma, hilus-cell tumor, and adrenal-rest tumor. The androgens produced by these growths do not cause an elevated excretion of the total 17-ketosteroids, just as in the Stein-Leventhal syndrome, but the growths are very rare, are unilateral, and are usually associated with other signs of virilism rather than just hirsutism. The diagnosis of hyperthecosis of the ovary, a condition responsive to wedge resection, is made only after histologic study of the resected ovarian tissue. Here, too, the patient shows a more marked degree of virilism than is seen in the Stein-Leventhal syndrome.

Perhaps the only pituitary condition to be seriously considered in a differential diagnosis is Cushing's disease, especially in its early stages. The clinical picture and characteristic hormone findings will easily rule out this disease. Furthermore, in comparison to Cushing's syndrome, it is a rarity.

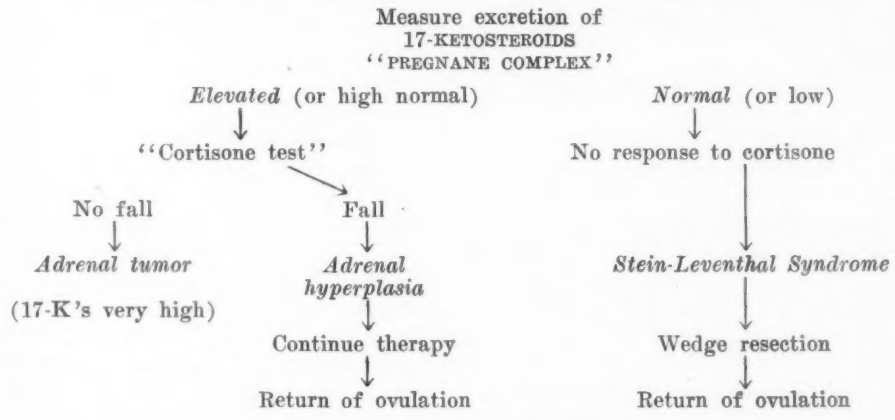
In the adrenal gland, hyperadrenalism due to overactivity of the cortex in the glucocorticoid sphere (Cushing's syndrome) is marked by disturbances in electrolyte and carbohydrate, fat, and protein metabolism. The clinical picture is typical, and there is an increased excretion of 17-hydroxycorticosteroids. Hyperadrenalism due to lesions involving the androgenic sphere (hyperplasia or tumor) is very important in the differential diagnosis of the Stein-Leventhal syndrome. There is an increased excretion of the 17-ketosteroids as well as of pregnanetriol.[27, 28] When such a lesion is present, wedge resection of the ovaries would, of course, be of no avail in therapy. The re-establishment of normal menstrual cycles following the administration of cortisone or its derivatives in adrenal hyperplasia (cortisone test) is an important differential diagnostic point inasmuch as cortisone has no effect whatsoever on the Stein-Leventhal ovary. The cortisone acts by inhibiting ACTH production, which is followed by a decrease in 17-ketosteroid and pregnanetriol excretion. This in turn "triggers" the pituitary gonadotrophins to act physiologically on the affected ovaries. On the same basis, another test may be a valuable diagnostic aid. When ACTH is administered to patients with adrenal hyperplasia, there is a hyperactive elevation of 17-ketosteroid and pregnanetriol excretions (ACTH test). Wilkins[29] was one of the first to use the cortisone suppression effect on ACTH in the treatment of patients with congenital adrenal hyperplasia. Later it was used in the acquired (or latent congenital) form of postpubertal adrenal hyperplasia.[30] In this latter condition, the degree of hyperplasia may be marked, producing the adrenogenital syndrome with greatly elevated 17-ketosteroids and distinct signs of virilism. Similar findings may occur with tumors (adenoma or carcinoma) but the latter do not respond to cortisone since they secrete independently of ACTH. The adrenal hyperplasia may be due to a minor defect with small and subtle degrees of dysfunction. It is this type that is found in the largest group of women with hirsutism who present themselves for differential diagnosis, and Gold[32] has used the term "borderline adrenal hyperplasia" to identify it. In these "borderline cases" diagnosis may be difficult since the ovaries may not be significantly enlarged, the hirsutism is mild, and the menstrual irregularities, although anovulatory, follow no definite pattern. Some patients may have regular menses, although oligomenorrhea is most prevalent. The 17-ketosteroids may be normal or slightly elevated, but there is an elevation in the excretion of the "pregnane complex" due to pregnanetriol.

Gold and Frank[32] administered prednisone as a therapeutic-diagnostic test to a group of these patients. According to them, if the "pregnane complex"

is elevated beforehand and then falls after the administration of cortisone, a presumptive diagnosis of "borderline adrenal hyperplasia" may be made. They place much importance on the elevated "pregnane complex" in diagnosis in spite of normal 17-ketosteroid excretions. They have accumulated a series of 23 patients with "borderline adrenogenital syndrome." Fifteen of the married women complained of infertility, all had varying degrees of hirsutism, and 9 had definite bilateral polycystic ovaries. Menstrual irregularities included amenorrhea or oligomenorrhea in two thirds of their patients, and menometrorrhagia or normal menses in one third. All were anovulatory, and all had an elevated "pregnane complex" excretion. The suspected patient was placed on prednisone, 30 mg. daily, for 3 days. If urine excretion studies of the "pregnane complex" showed a drop in value, the patient was given 10 mg. daily for 3 months during which time she was observed for evidences of ovulation. Normal ovulatory menstruation returned in 19 patients, and 9 patients became pregnant. Four of these had polycystic ovaries. Between the group of patients with overt adrenal hyperplasia and those with borderline changes there must be patients with varying degrees of hyperplasia. Jones and Jones[33] reported upon 16 patients with postpubertal oligomenorrhea (anovulatory), hirsutism, and elevated urinary 17-ketosteroids, all of whom had a drop in the 17-ketosteroids and a resumption of ovulatory menstruations following cortisone therapy. Five of 10 infertile patients in this group became pregnant. They also studied a similar group, with normal urinary 17-ketosteroids, who responded to cortisone therapy. Pregnanetriol excretion studies were made before therapy on 3 patients in this latter group, and all showed an elevation.

TABLE I

BILATERAL POLYCYSTIC OVARIES; AMENORRHEA; HIRSUTISM



Buxton and Vande Wiele[17] reported 17-ketosteroid determinations in 26 patients subjected to wedge resection. In 23 cases, the 17-ketosteroids were normal, and in 3 they were repeatedly elevated. The latter 3 patients failed to respond to operation. They also reported 3 cases of enlarged ovaries, hirsutism, and persistent anovulation, treated by 50 mg. of cortisone daily for 30 days. There was no thermogenic response and the clinical symptoms were unchanged. On the assumption, therefore, that the symptoms were not due to adrenal pathology, the 3 were subjected to wedge resection and normal ovulatory cycles occurred postoperatively. It is possible that the two syndromes (adrenal hyperplasia and the Stein-Leventhal syndrome) overlap and may be due to a common instigating factor (LH?). A break in the chain at either end may lead to homeostasis. A few of our patients who displayed

some increase in the excretion of 17-ketosteroids and pregnanes have responded to wedge resection. These were the ones who displayed the most marked degrees of hirsutism and their ovaries showed the most marked degrees of luteinization (Table I).

In summary, the importance of unhurried study of each patient before resorting to surgery cannot be overemphasized. If the 17-ketosteroids or the "pregnane complex" or both are elevated and the patient responds to prednisone therapy, a working diagnosis of adrenal hyperplasia is established, and proper therapy should establish ovulation. If the excretion products are normal with typically enlarged ovaries, the working diagnosis is the Stein-Leventhal syndrome, and the probability of a good response to wedge resection is great. In doubtful cases, a trial of prednisone therapy is advisable, and, if it is marked by failure, then wedge resection may be indicated.

Endometrial Carcinoma and Bilateral Polycystic Ovaries

There have been many reports in the literature suggesting a causal relationship between endometrial carcinoma and bilateral polycystic ovaries. It has been postulated that the hyperplastic theca, through elaboration of "chronic" doses of estrogen, could have an effect on the endometrium similar to that seen in some cases of granulosa-cell tumor. Speert[34] in 1949 reported on several young women with endometrial carcinoma who had the syndrome and since then others have reported similar observations.[35-38] Many of the cases reported have not been well documented and the true diagnosis of the syndrome remained unsubstantiated. Some cases were studied from autopsy material where polycystic ovaries were found, but whether these were truly clinical cases of Stein-Leventhal syndrome is open to question. The Stein-Leventhal syndrome is rare, and carcinoma of the uterus under age 40 is rare. In our combined experience, Stein and I have never seen endometrial carcinoma in association with the syndrome. Evidence of association is certainly not conclusive.

Treatment and Results

The treatment of sterility due to the Stein-Leventhal syndrome is wedge resection of the polycystic ovaries. There are some who have used low-dosage irradiation to the ovaries in patients who exhibit the syndrome, with establishment of normal menstruation and pregnancies. Rakoff[39] reported upon 5 patients who he thought had the syndrome and who elected irradiation instead of surgery. The ovaries were only slightly enlarged and culdoscopy on 2 patients showed the typical thick white capsules. All had hirsutism with normal 17-ketosteroids, and all failed to respond to hormone therapy including cortisone. Two patients showed a prompt response and became pregnant within a few months after irradiation. Two other patients had improved menstrual cycles with evidences of occasional ovulation, and the fifth patient showed no improvement. He states he would limit the use of irradiation to early cases, refractive to hormone therapy, in which the ovaries are only slightly enlarged. It may be advisable to suggest low-dosage irradiation to patients who fear or refuse operation, if the gynecologist does not fear or refuses to heed the warnings of geneticists about future mutations. A trial of prednisone in suspected cases is valuable in ruling out and treating cases of adrenal hyperplasia, thus helping in the selection of cases for wedge resection.

Up to the present time, Stein[40] has operated on 96 women with polycystic ovaries of the Stein-Leventhal syndrome. Normal menstrual function was established in over 95 per cent of his cases. He deleted 25 patients from his

statistics (8 single, 9 cases of male sterility, 1 who had had a hysterectomy, 1 divorced, 2 using contraception, 2 deceased, 2 no follow-up) leaving 71 women to be followed regarding fertility. Of these, 63 or 88.7 per cent became pregnant one or more times. He noted no recurrences of the ovarian pathology. There were no ectopic pregnancies, and he has never noted an associated endometrial carcinoma. One patient, whose husband was azoospermic, became pregnant twice by donor insemination. Although the series reported by Leventhal and Cohen (10 cases) is too small to be statistically significant, nevertheless 5 out of 6 married women became pregnant after wedge resection. The duration of infertility in this group varied from 3 to 7 years. Two of the 4 single women in this series became pregnant following operation. Six of the 8 infertile patients on whom I have operated since 1948 have had pregnancies following wedge resection. Since the ovarian changes become static, do not as a rule cause discomfort, and can always be treated surgically at a later date, I have on occasion advised young single girls to do nothing until such time as they are married and desire children. The operation, of course, should be done at any time if normal menstruation is desirable for emotional reasons. Patients on whom bilateral ovarian wedge resection was performed have been followed for as long as 25 years without signs of recurrence. At cesarean section and during hysterectomy we have had the opportunity of examining ovaries previously resected and have found them normal in appearance. Occasionally postoperative adhesions at the site of operation have been noted, but these can be obviated by meticulous closure of the ovarian incision (Table II).

TABLE II. RESULTS OF WEDGE RESECTION IN THE STEIN-LEVENTHAL SYNDROME AT MICHAEL REESE HOSPITAL

	OPERATIONS	INFERTILITY FOLLOW-UP	PREGNANT	%
Stein	96	71	63	88.7
Leventhal and Cohen	10	8	7	87.5
Leventhal	8	8	6	75.0
Total	114	87	76	86.2

Summary

This review of the Stein-Leventhal syndrome was undertaken in order to crystallize our present knowledge about it. Although the pathogenesis has not been established, it is considered a possibility that the ovarian changes are due to a "chronic" stimulation by LH. It is possible that the adrenal cortex as well as the ovaries may be involved in the symptomatology in some cases, but this association has not been clarified. Of the many conditions producing amenorrhea, enlarged ovaries, and hirsutism, which must be differentiated from the Stein-Leventhal syndrome, mild adrenal hyperplasia is most important. Determinations of the urinary excretions of the 17-ketosteroids and the "pregnane complex" and the use of the "cortisone suppression" test are valuable aids in the selection of patients for wedge resection.

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THE FINE STRUCTURE OF THE BASEMENT MEMBRANE OF THE UTERINE CERVICAL EPITHELIA*

Observations With the Electron Microscope

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THE basement membrane of the human cervical epithelium has been the subject of as much controversy as any other histological component of that organ. Using light microscopy investigators have found it to be definitely present[1] and definitely absent.[2] It has been stated to be penetrated or not penetrated in almost every reported study of early cancer of the uterus. Schiller and associates[2] made a detailed study of the method of attachment of the cervical epithelium to the underlying stroma, concluding that there was no basement membrane and that basal cells were secured by fibrils penetrating the connective tissue. It would be pointless here to summarize opinions of and evidence submitted by the many investigators of the basement membrane; suffice it to say that there is divergence of views and that more evidence gathered by more inquiring means is required to determine the nature of this junction.

An investigation has been instituted utilizing the electron microscope, to study the nature of the cervical epithelium-stroma junction in normal and disease states. This particular report deals with findings in normal tissue and is a necessary prelude to the study of tissue altered by disease.

Review of the Literature and Prior Studies

There are no published studies of the fine structure of the human cervix. A number of excellent reports have appeared, however, detailing the ultrastructure of skin,[3, 4, 5] ciliated epithelia of Mollusca, Amphibia, and mammals,[6] basement membranes of kidney epithelium and endothelium,[7] and the basement membrane of lung.[8-12] With modifications, some of these observations are valid for corresponding tissues of the cervix.

Selby[4] described a dermal membrane (basement membrane) of skin epithelium which is submicroscopic in thickness (300 A), composed of parallel electron dense layers above and below a clear zone. The membrane is homogeneous, not made up of recognizable fibers or filaments. There is an arrangement

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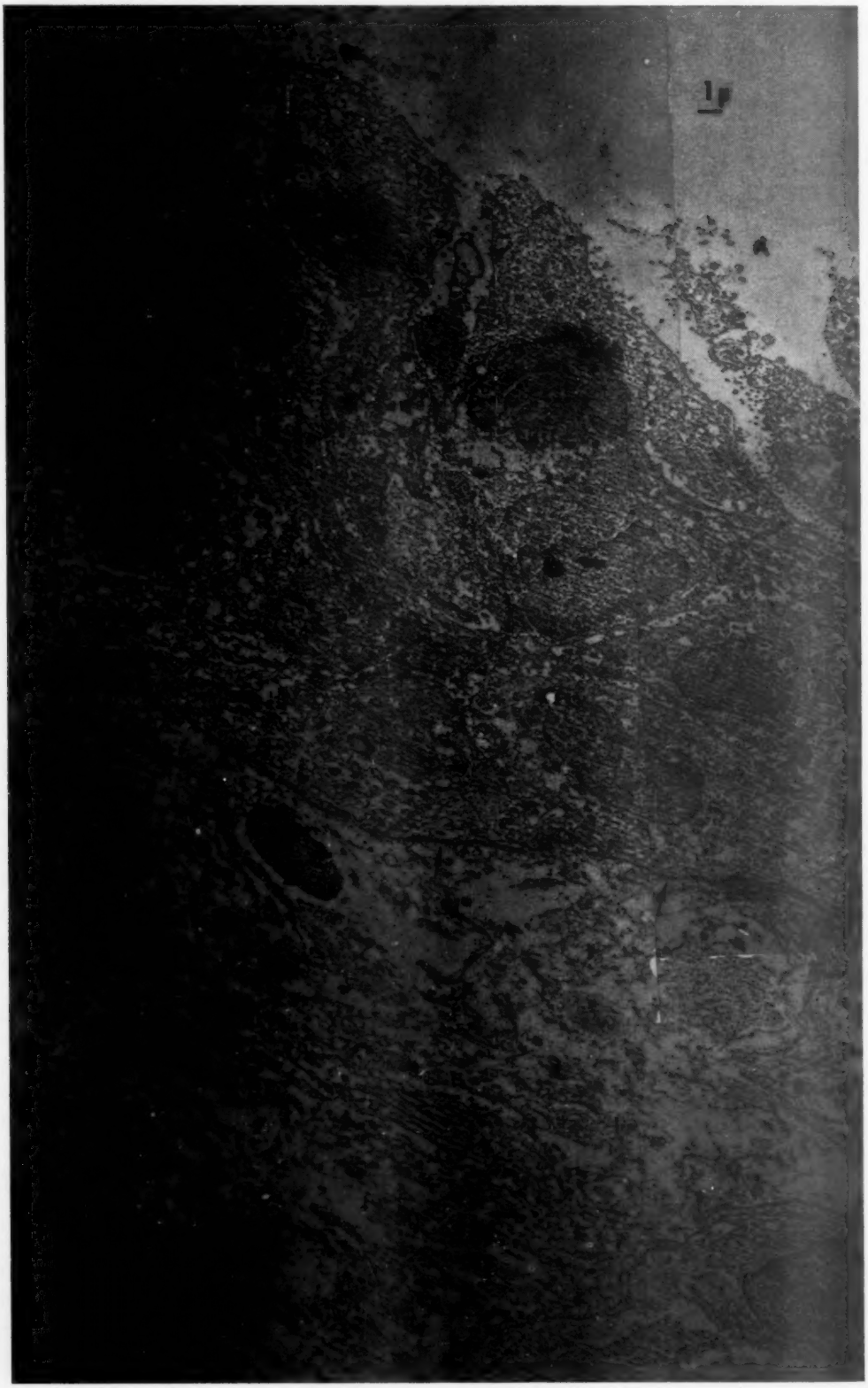
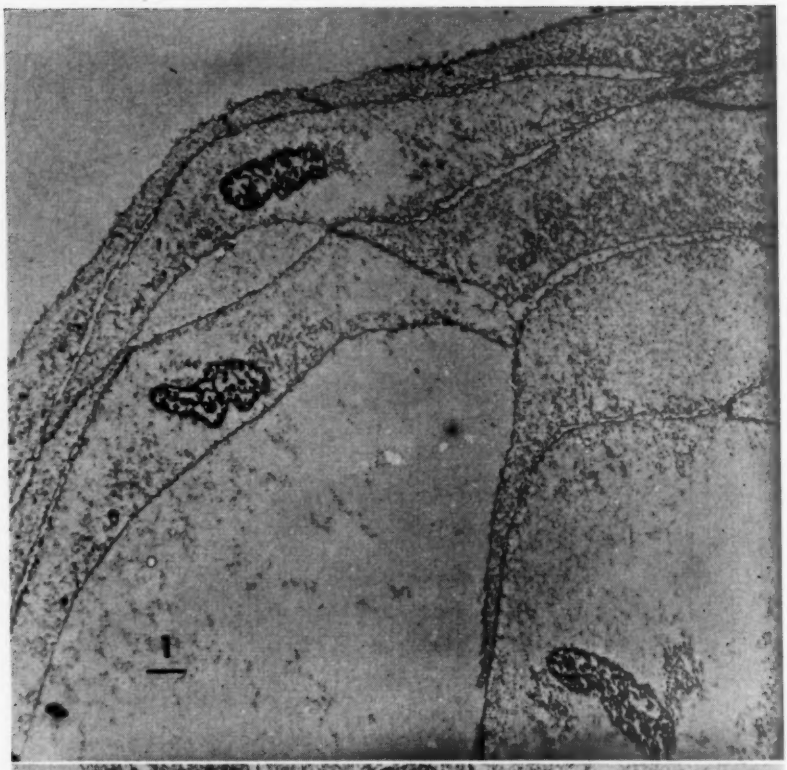


Fig. 1.—Mosaic electron micrograph of cervical stratified squamous epithelium and its junction with cervical

tion with cervical stroma. (×5,600, reduced ½. Micron marks appear on this and all other micrographs.)

Fig. 2.



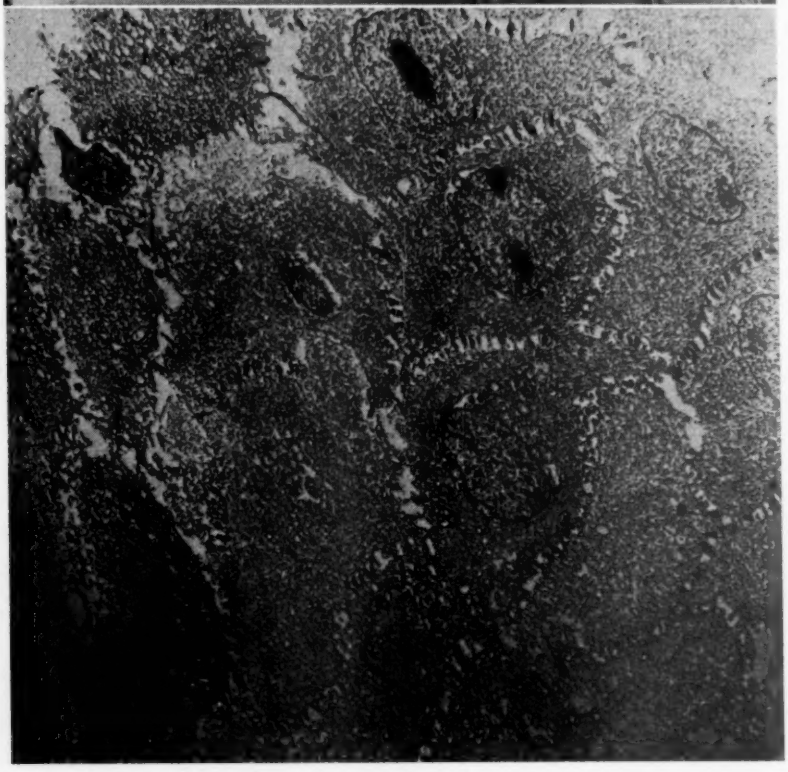


Fig. 3.

Fig. 2.—Cornified and precornified cells of the outer epithelial layers. (×8,000, reduced.)
Fig. 3.—Prickle cells of the stratum spinosum. (×8,000, reduced.)

of narrower collagen fibers adjacent to the membrane on the connective tissue side, and a suggestion superficially of cement substance between epithelial cell membranes and dermal membrane.

Cilia are known to be present in endocervical cells (Papanicolaou, Traut, and Marchetti[13] and bibliography). Fawcett and Porter[6] pointed out that cilia in specimens of several different types of animals have the same ultrastructure. That is, the cilium is composed of nine peripherally arrayed filaments grouped around a pair of central filaments. This make-up was noted in cilia of the human endosalpinx. The same investigators also noted that the columnar epithelium in Amphibia rested on a continuous thin membrane.

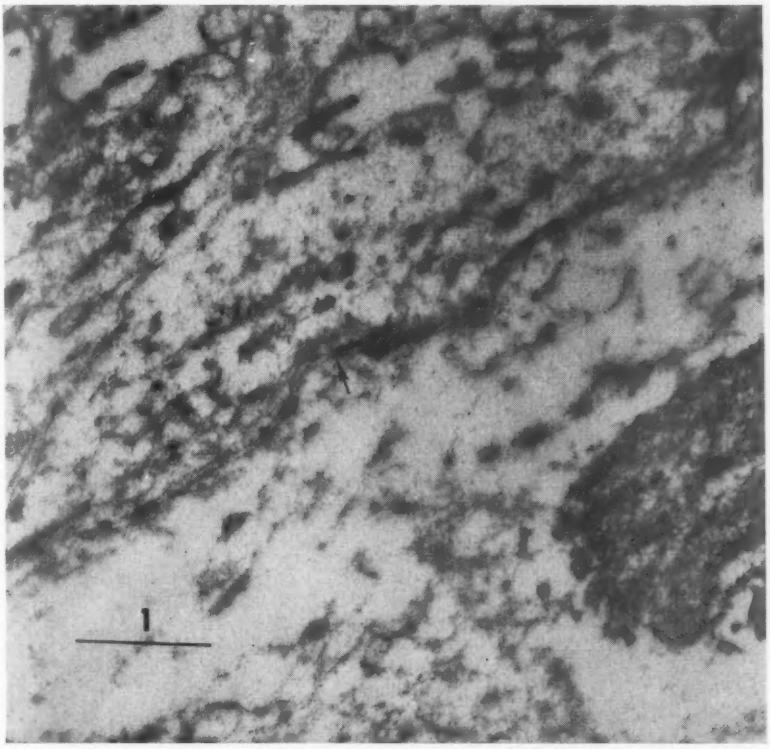


Fig. 4.—Basement membrane of the stratified squamous epithelilum. Average thickness of the membrane is 300 A. (×41,400, reduced.)

Basement membranes have been found separating alveolar epithelium of the lung and capillary endothelium,[9] and between epithelial processes and endothelium of kidney glomeruli.[7] In both of these locations the submicroscopic membranes have an inner and outer dense layer with a lucent center portion. They are apparently devoid of fibrous elements, being of a homogeneous make-up.

Methods of Study

The tissue in this study was secured by cervical biopsy from patients in the Cancer Detection Clinic, Louisiana State University Obstetrical and Gynecological Service, Charity Hospital of New Orleans. Normal tissue was obtained from patients whose cervices were found to be entirely without abnormality under the colposcope. After removal by punch biopsy, a specimen was

Fig. 5.

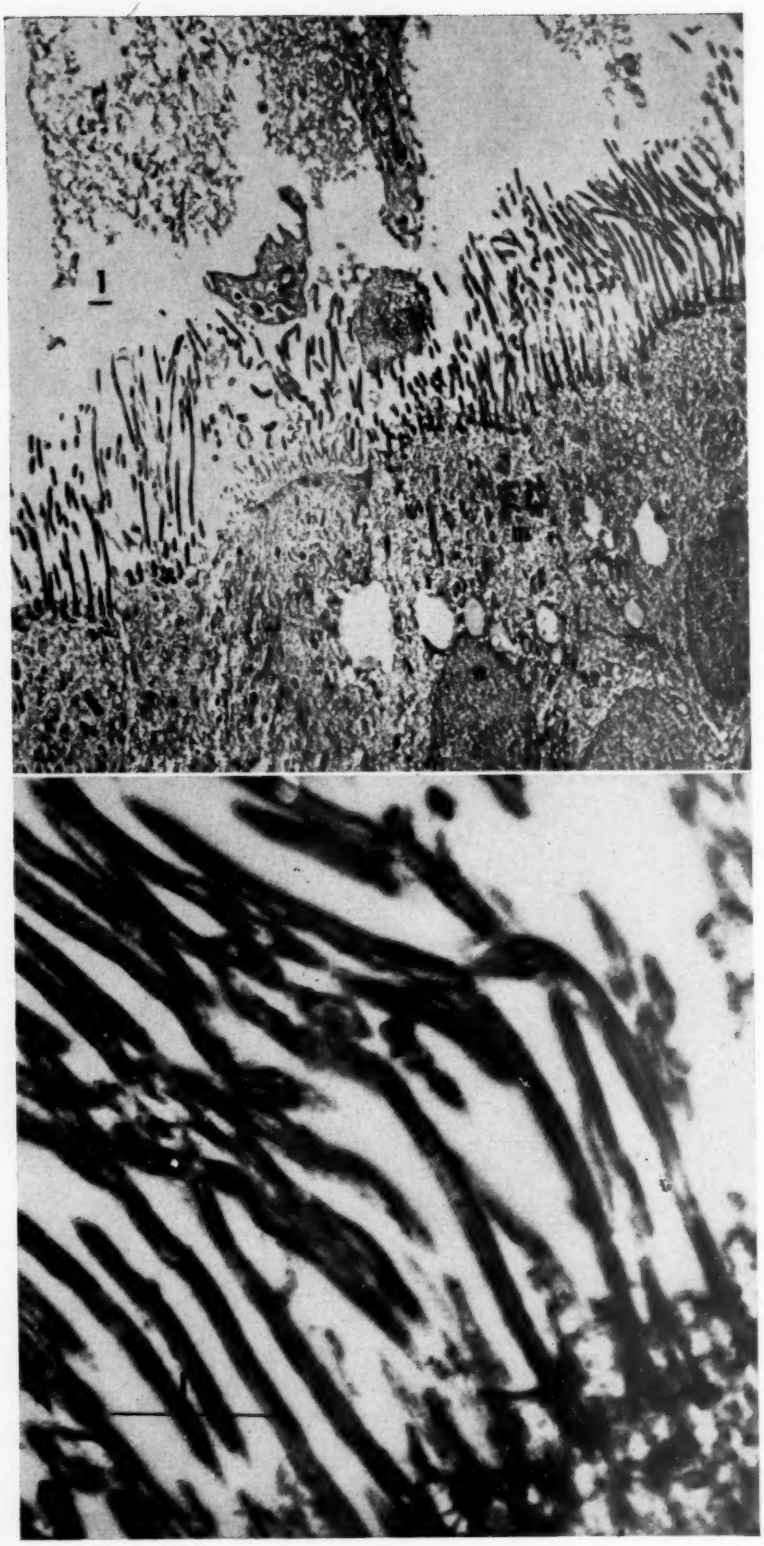


Fig. 6.

Fig. 5.—Endocervical columnar epithelium, cilia (*c*), mitochrondria (*m*), cell nuclei (*n*). (×5,600, reduced.)

Fig. 6.—Each cilium of endocervical epithelium is seen to be made up of several filaments or rods. (×41,000 reduced.)

divided longitudinally, half being fixed in Bouin's solution for light microscopic preparation, and half placed in osmic acid fixative for use in the electron microscope.

A major problem was that of proper orientation of the specimen. Because all tissue is rendered uniformly black by osmic acid, the epithelial surface cannot be distinguished and gross visual orientation is not possible. It was therefore found to be necessary to trim the specimen in a particular shape so that it exhibited an identifiable long dimension. When the tissue was cut at a right angle to its long axis a perpendicular section through the epithelium-stroma junction was obtained. After proper orientation of specimens was accomplished, critical study of the junction was possible.

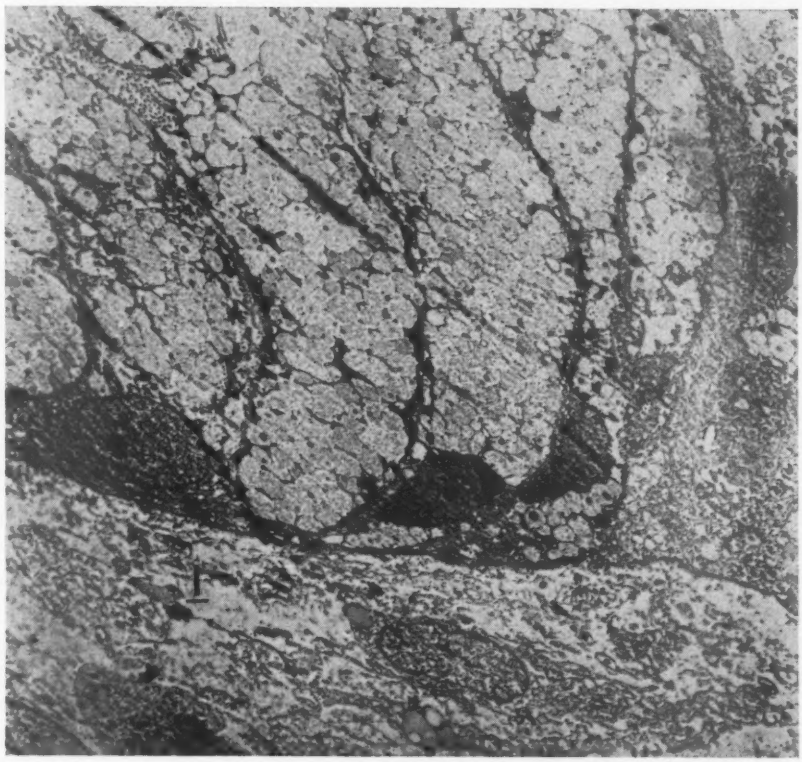


Fig. 7.—Endocervical cells containing secretory globules. (×5,600, reduced.)

Observations

The major features of the ultrastructure of the normal cervix are pictured in the accompanying illustrations. The general appearance of stratified squamous epithelium, junction, and cervical stroma can be seen in Fig. 1, which is a mosaic of nine separate electron micrographs. The basal half of the epithelium is present in this illustration, the outer half of the layer having been removed in collecting. A basement membrane courses the entire distance of the epithelium-stroma boundary (detail seen in Fig. 4). The ragged-appearing stroma is composed of a variety of elements the details of which will be exhibited in subsequent micrographs.

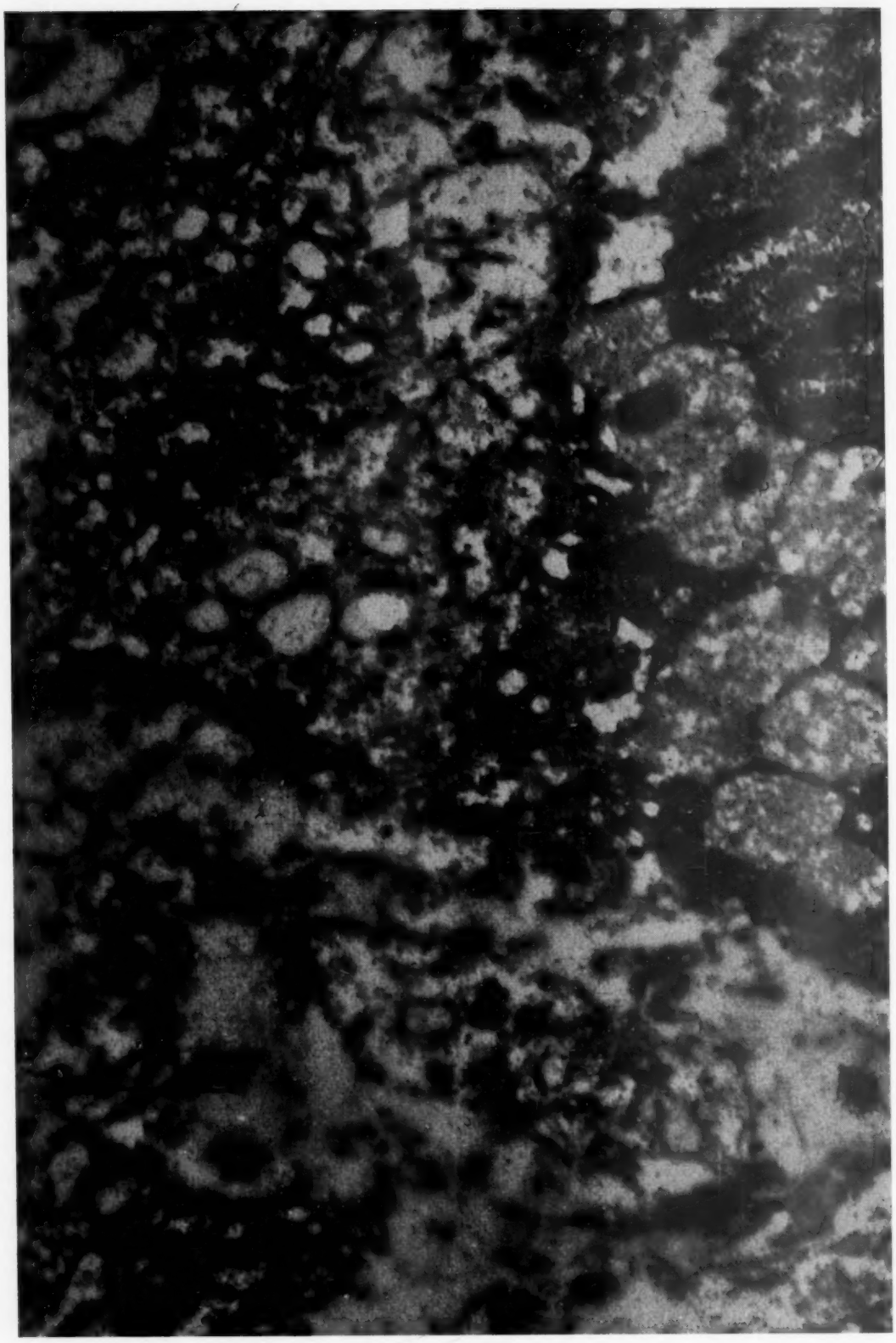


Fig. 8.—Basement membrane of the columnar epithelium, enlarged from the preceding figure. (×22,600, reduced.)

Fig. 9.—Fascicle of smooth muscle cells invested by a thin membrane. (×5,600, reduced.)

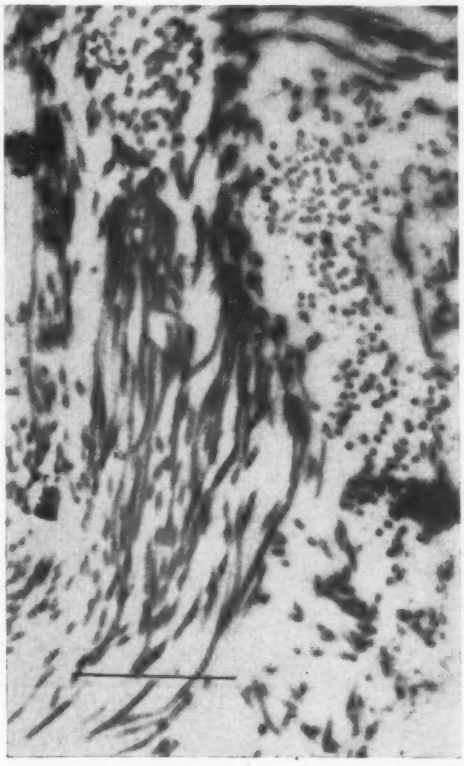


Fig. 10.—Collagenous fibrils with typical banded structure. (×41,000, reduced.)

Fig. 11.

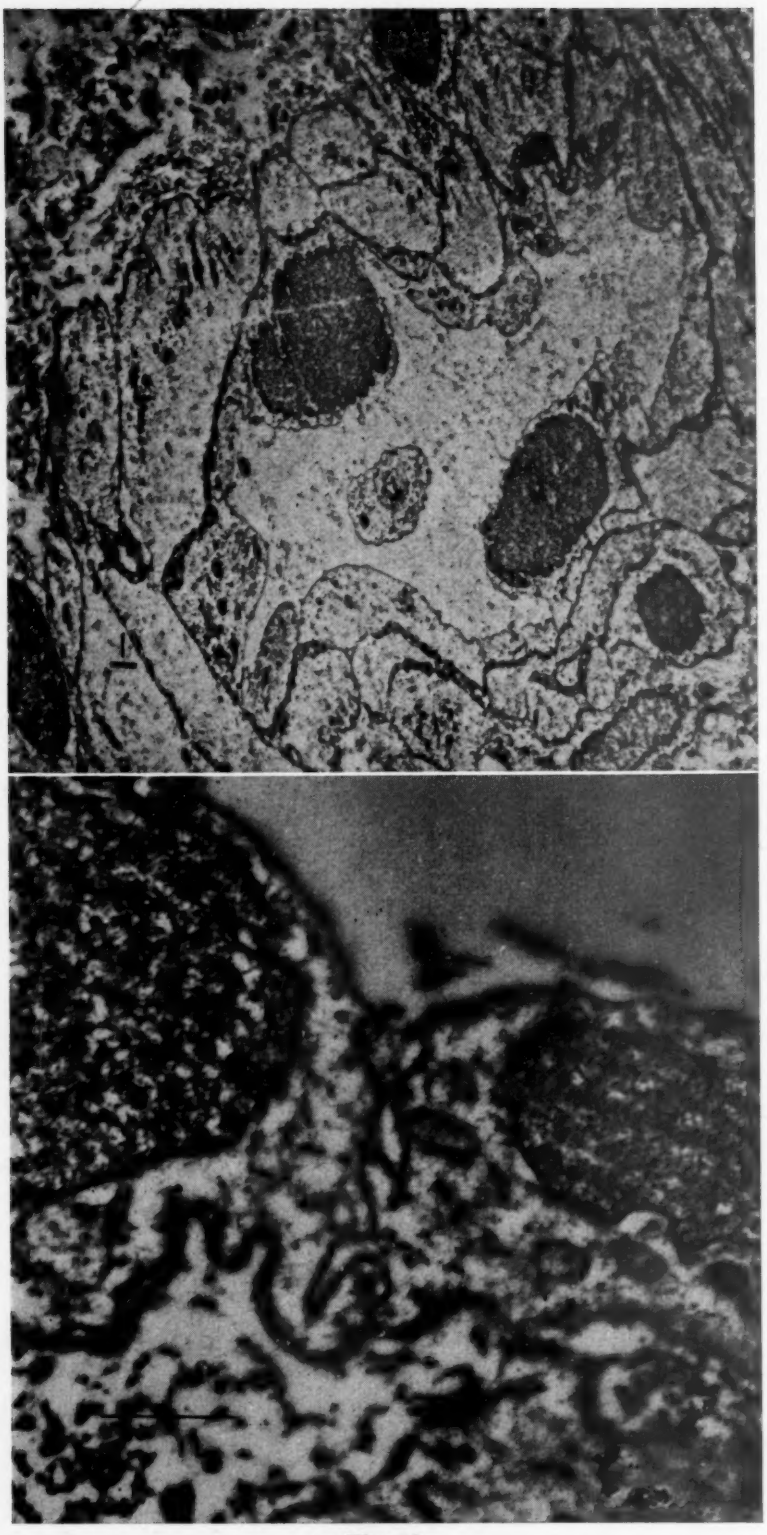


Fig. 12.

Fig. 11.—Endothelium-lined space with wall of smooth muscle. This is most probably a small arteriole. (×5,600, reduced.)

Fig. 12.—High magnification of the membrane surrounding endothelium of a vascular space. (×33,400, reduced.)

Lower magnifications of the electron microscope reveal characteristics similar to those noted by the light microscope. Cornified and precornified squamous cells (Fig. 2) resemble those prepared by paraffin with hematoxylin and eosin stain. Prickle cells (Fig. 3) very clearly show intercellular bridges, with nodes of Bizzozero midway between cells, cytoplasm, nucleus with nuclear membrane, nucleoli, and chromatin material. The basement membrane of the stratified squamous epithelium can be demonstrated as a double-layered structure (Fig. 4), continuous from one side of the specimen to the other, and perfectly intact in the normal cervical epithelium. The structure here demonstrated is 300 A wide and therefore not visible with the light microscope.

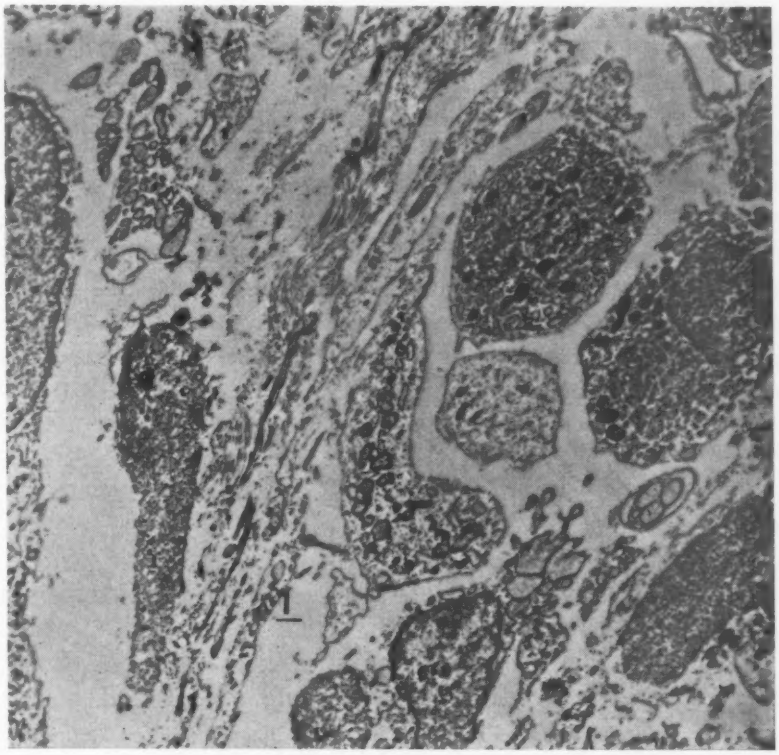


Fig. 13.—Plasma cells in cervical stroma. (×5,600, reduced.)

Endocervical epithelial cells exhibit typical cilia (Fig. 5) at their periphery, detailed scrutiny of which at high magnification (Fig. 6) reveals each cilium to be made up of several smaller filaments—a characteristic of cilia in general.[6] Cross section of cervical columnar cells (Fig. 7) displays many secretory globules contained in the endoplasmic reticulum. Nuclei are basal, though some cells have globules beneath the nuclei at the very base of the cell. The basement membrane of the columnar epithelium is similar to that of the stratified squamous epithelium. It is composed of two parallel electron dense laminae arranged very close together and it is literally intact (Fig. 8).

Cervical stroma is made up of several elementary tissues. Bundles of smooth muscle cells can be seen (Fig. 9) sometimes enveloped in a thin membrane which appears to contribute secondary septae to surround each cell.

Typical collagenous fibrils with beaded or banded structure (Fig. 10) are abundantly in evidence. Many endothelium-lined spaces and small blood vessels lace the stroma (Fig. 11), each of which can be seen to have a well-defined basement membrane (Fig. 12) of double-laminar architecture. There is nearly always, in the parous cervix, a degree of inflammatory infiltration. Several inflammatory cells are depicted in the micrograph in Fig. 13. The two oval cells, one with nucleus, are plasma cells. Hairlike collagenous tissue fibrils are seen extending diagonally across this photograph.

Summary and Conclusions

A basement membrane of the cervical stratified squamous and columnar epithelia can be demonstrated under the electron microscope as a continuous and intact structure separating these layers from the underlying stroma. A basement membrane can also be demonstrated surrounding many of the endothelium-lined vascular spaces in the cervical stroma. The thickness of these membranes is 300 A or 0.03 μ, far too thin to be seen by light microscopy.

Although the membrane found by electron micrography is located in the same relation to epithelium as that demonstrated by PAS and reticulum stains in paraffin sections for light microscopy, the two are not identical structures. The electron dense structure undoubtedly forms part of the membrane seen in normal histological preparations. Exactly what relationship exists is not known since the membrane seen by electron microscopy is beyond the limit of resolution of the light microscope.

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OVARIAN ESTROGENIC TUMORS AND DIFFUSE ESTROGENIC THECOMATOSIS IN POSTMENOPAUSAL COLPORRHAGIA

The Importance of the Benign Endometrial Mitosis

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THE increased span of life in recent decades has brought into prominence many problems of geriatrics among which postmenopausal vaginal bleeding has become of pressing concern. Iatrogenic vaginal bleeding due to administered estrogen as well as blood dyscrasias must always be considered and dealt with appropriately. Lesions of the cervix and fundus of the uterus such as chronic inflammation, nonneoplastic ulcerations, polyps, submucosal leiomyomas, malignant tumors, and atrophic endometrium which cause vaginal bleeding may be diagnosed without too much difficulty and proper therapy carried out. The value of an exploratory operation for colporrhagic postmenopausal women with a pelvic mass and an estrogen-stimulated endometrium cannot be disputed. An encounter, however, with a postmenopausal colporrhagic woman with a nonpalpable estrogenic ovarian tumor and proliferating endometrium led to the discovery that an active and prolonged controversy had arisen in the literature regarding the feasibility of an exploratory laparotomy in this type of patient. In an attempt to aid in the solution of this problem, the records of 140 cases of postmenopausal hemorrhage in women over 60 years of age who had been curetted in a community hospital were reviewed and, among those without endometrial carcinoma, there were found to be 5 cases of estrogen-secreting ovarian tumors and one case of diffuse ovarian thecomatosis. The presence of active estrogen secretion was indicated by the finding of benign endometrial mitoses with hyperplasia. No exogenous estrogen had been administered to any of these 6 patients. A study of these postmenopausal women with prolonged amenorrhea, some of whom had no palpable pelvic masses, led to the belief that publication of the clinical and histopathologic details found would be of value particularly in aiding those concerned with this type of case to decide whether an exploratory laparotomy is indicated.

In the above 140 postmenopausal women over 60, apart from the 6 patients analyzed in this report, there were 100 patients in whom no malignant tumors of the genitals could be found. The latter consisted of those with postmenopausal periods of amenorrhea of more than 3 years who had received no exogenous estrogen. In none of these could a benign endometrium with mitotic

figures and no active estrogenic ovarian lesion be found. One colporrhagic woman of 61 years without a palpable pelvic tumor who was not subjected to a laparotomy was curetted after a postmenopausal amenorrhea of 6 years and the benign endometrium contained mitotic figures. She was followed for 4 years after the curettage during which time no further bleeding occurred. This problem of cessation of bleeding after curettage despite the possible presence of an active estrogenic ovarian lesion will be considered later.

Clinical Data

CASE 1.—This 61-year-old white woman had a menopause 11 years before the last admission. A uterine suspension and a right oophorectomy had been done 33 years before and a radical mastectomy 5 years before. Two to 3 months before the last admission, painless vaginal bleeding occurred once a month and lasted 2 days each time. About 5 days before the last admission, this bleeding became more abundant and continuous and was accompanied by left lower quadrant, cramplike, abdominal pain. On pelvic examination, a moderately tender mass of indefinite size and shape was palpated. Curettage revealed smooth, glistening, grayish-pink tissue. A total hysterectomy and left salpingo-oophorectomy were done. A diagnosis of a thecoma of the left ovary was made.

CASE 2.—This 60-year-old white woman had a menopause 12 years before the last admission. Four years before the last admission, vaginal bleeding occurred for 2 hours the night before she entered the hospital. Pelvic examination at that time revealed a globular, slightly enlarged uterus. No adnexal masses were felt. Curettage yielded a scanty amount of endometrium. For 6 weeks prior to the last admission, moderate vaginal bleeding had occurred. Pelvic examination at the time of the last admission disclosed a firm, movable, left adnexal mass and curettage at this time yielded a scanty amount of endometrium. Shortly after the curettage, a total hysterectomy and a left salpingo-oophorectomy were done. A diagnosis of a thecoma of the left ovary was made.

CASE 3.—This 60-year-old white woman had a menopause 2 years before admission. Painless vaginal bleeding had occurred 2 weeks previously and had persisted until the day before admission. Pelvic examination disclosed a mass in the anterior wall of the uterus which proved to be a leiomyoma but no adnexal mass was detected. A curettage yielded a moderately abundant mass of tissue and a total hysterectomy and bilateral salpingo-oophorectomy were performed. A diagnosis of a mixed granulosa- and theca-cell tumor was made.

CASE 4.—This 75-year-old white woman had experienced regular periods prior to the menopause which had occurred 26 years before the last admission. A year after that, a uterine suspension was done intra-abdominally and no ovarian lesions were observed. A curettage at that time yielded an inactive endometrium. Two years before the last admission, a left radical mastectomy was performed for adenocarcinoma. One year later, vaginal bleeding had occurred for 4 days and curettage yielded a small amount of endometrium measuring 0.6 cm. in diameter and a diagnosis of cystic hyperplasia with mitoses was made. No pelvic masses were detected at that time although examination was hindered by the obesity of the patient. No further surgery was contemplated because of hypertension, cardiac infarction, and left ventricular failure during the previous 3 years. No further vaginal bleeding occurred after discharge from the hospital. Two weeks before the last admission, vomiting and abdominal cramps occurred. The pain became localized in the right lower quadrant and became more severe 9 days later. On the night before she entered the hospital, an acute episode of abdominal pain was accompanied by right lower quadrant spasm and tenderness. On rectal examination, a firm, tense pelvic mass was noted. A right salpingo-oophorectomy was done and a diagnosis of an infarcted mixed granulosa- and theca-cell tumor was made. The patient left the hospital in good condition and continued so for 1½ years when she was last seen.

CASE 5.—This 60-year-old white woman had regular periods prior to the menopause and subsequently complete amenorrhea for 15 years. About 9 days before admission to the hospital, vaginal bleeding began and lasted for 3 days. A pelvic examination was negative. A curettage was done and then a total hysterectomy and a bilateral salpingo-oophorectomy were carried out. A diagnosis of mixed granulosa- and theca-cell tumor was made.

CASE 6.—This 64-year-old white woman had had a menopause 10 years before. Three months before admission she began to have vaginal bleeding which continued, requiring several pads a day. The flow was intermittent and sometimes consisted of a little brown spotting. Pelvic examination disclosed no pelvic mass. A curettage yielded a large amount of tissue suggesting malignancy. A total hysterectomy and salpingo-oophorectomy were done. A diagnosis of bilateral diffuse thecomatosis was made.

Fig. 1.

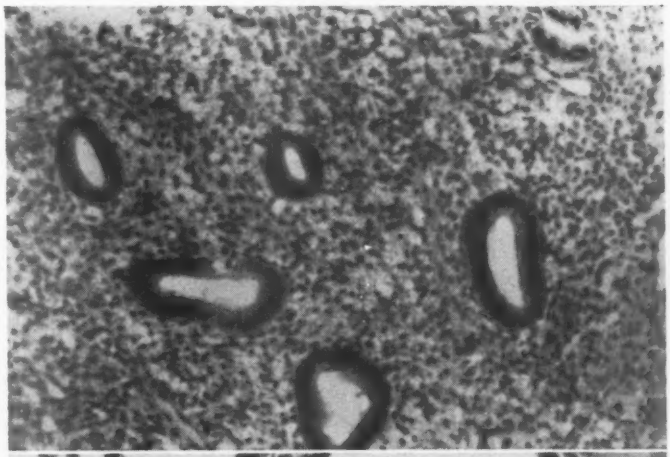

Fig. 2.

Fig. 1.—Case 5. Curetted endometrium. Note small straight glands lined by predominantly simple columnar epithelium found in scanty specimen. The stroma is nonfibrotic, cellular.

Fig. 2.—Case 5. Endometrium of extirpated uterus. Polypoid cystic, hyperplastic endometrium. Some of the glands are lined by pseudostratified columnar epithelium. Note contrast with Fig. 1.

Histopathologic Data

Gross.—The curetted endometrium in the first case of thecoma was abundant, while in the second it was scanty. In the first case of mixed granulosa- and theca-cell tumors, the

curetted endometrium was moderately abundant and in the other two scanty. On the other hand, the curettings in the case of thecomatosis were so abundant as to suggest cancer. In none of the cases were the uteri enlarged. One was 4.0 cm. in length and another measured 5.0 by 6.0 by 3.5 cm. In 2 cases, leiomyomas of the fundus were present, in one they were multiple and small and in another single and situated in the anterior wall of the uterus, forming a mass which was felt on pelvic examination, while the mixed granulosa- and theca-cell tumor also present was not palpable. Both thecomas were found in the left ovary and each formed a bilobated mass. Each lobe in the first case measured about 5.0 cm. in diameter and in the second 2.5 to 3.0 cm. in diameter. On section, they were composed of firm, solid, yellowish-gray fibrous tissue arranged in ill-defined whorls. Two of the mixed granulosa- and theca-cell tumors were found in the left ovary and one in the right. The mixed tumors varied from 5.0 to 11.5 cm. in greatest diameter and were usually indistinctly lobated with smooth surfaces varying from bluish white to grayish red. The infarcted tumor of Case 4 was dark reddish black. All 3 of the mixed tumors contained cysts, 1 was unilocular and had a thin wall 0.2 to 0.3 cm. in thickness, the others were multilocular with large amounts of compact tissue present. The compact tissue of 2 of the mixed tumors was yellow to yellowish brown, that of the infarcted tumor reddish black. Occasionally, narrow gray connective tissue trabeculae subdivided the tumor tissue into lobules. Both ovaries were involved in the case of thecomatosis and were small, measuring 1.3 by 0.7 by 0.4 cm. On section, the ovarian tissue was grayish yellow without undue prominence of the cortex.

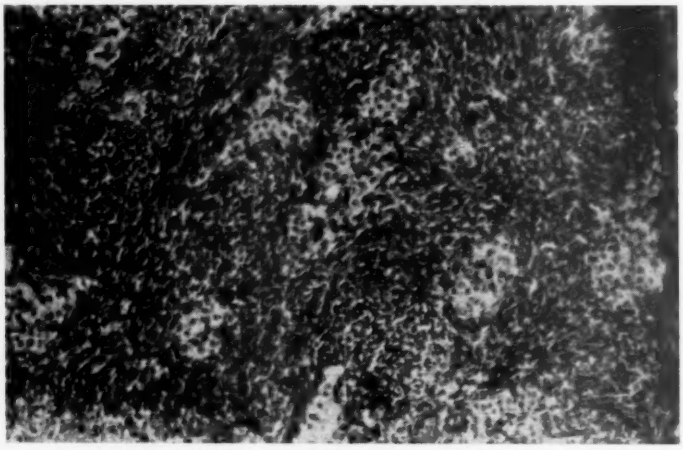

Fig. 3.—Case 2. Thecoma with groups of luteinized theca cells surrounded by spindle cells resembling ovarian stromal cells.

Microscopic.—The curetted endometria resembled those of the extirpated uteri except in Case 2 where the mitotic figures were found only in the endometrium of the extirpated uterus and in Case 5 where the curetted endometrium, apparently obtained from the superficial portion, was very scanty and resembled a youthful proliferative phase (Fig. 1) with small glands and simple columnar epithelium rather than the abundant polypoid, cystic hyperplastic endometrium of the extirpated uterus. In general, the following features indicating the presence of active cystic hyperplasia were found in all the endometria (Fig. 2). The glands were elongated, occasionally branched, at times cystic. The noncystic glands were lined by tall columnar cells with abundant cytoplasm and plump nuclei while the cystic glands were usually lined by flat to low cuboidal epithelium with scanty cytoplasm and small, hyperchromatic nuclei. Pseudostratification with small papillary projections was also observed. The stroma was often cellular with moderately plump, vesicular nuclei, but in a few regions the stroma was fibrotic and hypocellular and here the cystic dilatation of glands was most prominent. Polypoid structures composed of cellular and hypocellular fibrotic

tissue were observed. Most important of all, however, was the presence of mitotic figures in both the glands and stroma so that the statement that estrogen activity was present in all the endometria can be made with assurance.

The thecomas (Fig. 3) of Cases 1 and 2 were composed of intersecting bundles of spindle cells with scanty cytoplasm almost completely replacing the ovary. Some of the nuclei were plump. No mitotic figures were seen. Scattered hyaline trabeculae extended through the tumor. Occasional compact groups of polygonal cells were found surrounded by the spindle cells, and these cells possessed abundant delicately vacuolated cytoplasm suggesting epithelioid cells. In the vicinity of the ovarian remnants, a few cysts were observed lined by columnar cells with scanty cytoplasm as well as infrequent corpora albicantia completely surrounded by the tumor tissue.

Fig. 4.

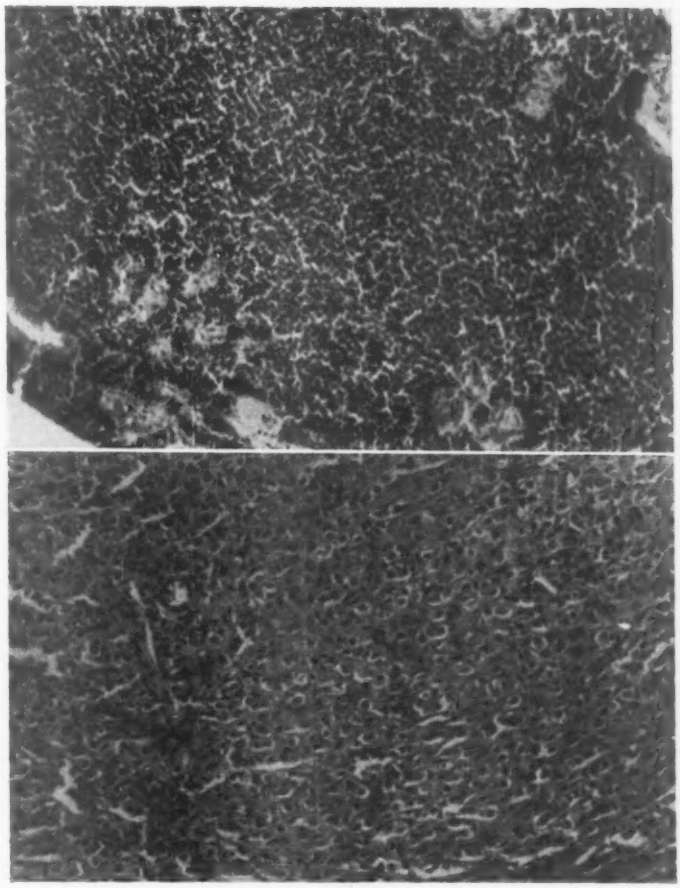

Fig. 5.

Fig. 4.—Case 3. Mixed granulosa- and theca-cell tumor composed predominantly of granulosa cells.

Fig. 5.—Case 5. Mixed granulosa- and theca-cell tumor composed predominantly of theca cells specifically responsible for types of endometrium in Fig. 1 and Fig. 2.

The mixed granulosa- and theca-cell tumors varied in the proportions of granulosa and theca cells. In Cases 3 and 4, there was a great predominance of the granulosa cells (Fig. 4) while the reverse held true in Case 5 (Fig. 5). The granulosa cells were usually arranged in solid sheets with oval to round nuclei containing scattered chromatin granules. Many of the nuclei were indented or wrinkled. The nucleoli were inconspicuous. The cytoplasm was

scanty and the cell borders ill defined. Little variation in size or shape of the nuclei was seen. There was, at times, palisading of the granulosa cells about blood vessels with the formation of pseudorosettes. The walls of the blood vessels were occasionally hyalinized and thickened. Cystic spaces were often seen in the sheets of granulosa cells and Call-Exner bodies were sometimes observed. Mitotic figures were found infrequently. Patches of hyalinized acellular connective tissue were present as well as narrow trabeculae of similar tissue enclosing groups of cells. In the infarcted tumor of Case 3, abundant necrotic hemorrhagic tissue was present with considerable hemosiderin and only a few viable masses of cells. The theca cells in these same tumors possessed round vesicular nuclei with prominent small nucleoli. The cytoplasm was abundant, vacuolated, and the cell borders more distinct than in the granulosa cells. In some of the tumors remnants of ovarian tissue were still present.

In the case of thecomatosis, in both ovaries diffusely arranged single and grouped polygonal cells with vesicular round nuclei containing small but prominent nucleoli were present (Fig. 6). The cytoplasm was abundant, acidophilic, and occasionally finely vacuolated. Infrequently, fine yellowish granular pigment was observed in the cytoplasm. The cortex was narrow and moderately cellular with only a few whorls present. No ova or developing follicles were seen. Follicular cysts were absent. Corpora albicantia were present but no connection of the theca cells with these structures was discerned. In fact, solitary theca cells were found surrounded by the spindle stroma cells suggesting transformation of the stromal cells into the theca cells. No superficial collagenization of the ovarian cortex was observed comparable to that found in the Stein-Leventhal syndrome. Occasionally, a thin, short segment of fibrous tissue was found along the surface of the cortex but this was attributed to previously ruptured follicles.

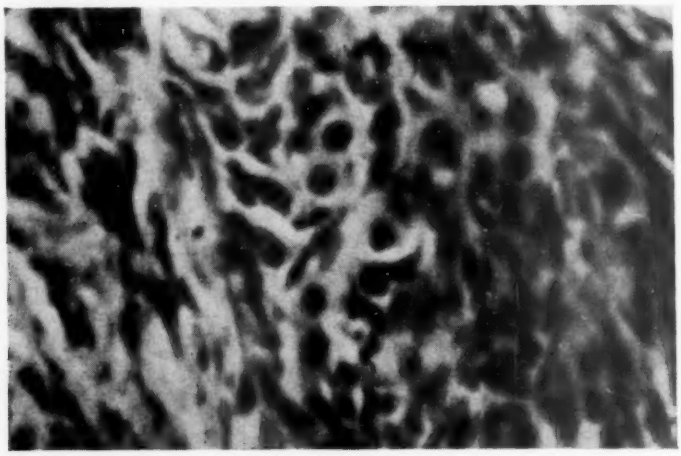

Fig. 6.—Estrogenic thecomatosis. Small groups of estrogenic theca cells with round nuclei, prominent nucleoli, and abundant cytoplasm distributed diffusely in ovarian cortex.

Comment

Estrogenic Ovarian Tumors.—The postmenopausal amenorrhea in the 5 cases of estrogen-secreting ovarian tumors reported above, except for one case of 2 years' duration, had lasted for 11 years or longer. The longest period of postmenopausal amenorrhea was 26 years in a 75-year-old woman. The vaginal hemorrhages which ended the period of postmenopausal amenorrhea at times assumed an episodic character but, in general, had no regular temporal pattern. It was usually painless. One woman had bled for only 4 days one year before the removal of an infarcted mixed granulosa- and theca-cell tumor and had stopped bleeding after a curettage. In another case, vaginal bleeding had occurred for 2 hours 4 years before the removal of a mixed granulosa- and theca-cell tumor and, after curettage at that time, had not recurred until 6 weeks

before oophorectomy when daily periods of vaginal hemorrhage required the use of a pad. These last 2 cases illustrate the possibility of a prolonged, even permanent, cessation of postmenopausal colporrhagia after curettage despite the presence of a persistently estrogen-secreting ovarian tumor. This cessation has been taken for proof by some authors that an estrogenic ovarian tumor was absent.

As for the types of tumors found in the present series, 2 were thecomas and 3 were mixed granulosa- and theca-cell tumors.

In 3 of the 5 tumors, no palpable adnexal masses were observed although one of these did become palpable after infarction. In one case, a mass palpated in the anterior uterine wall proved to be a leiomyoma. Obesity must be recognized as a factor in obscuring an ovarian tumor which might otherwise be palpable on pelvic examination, as in Case 4. In an evaluation of this type of case, the presence of mitotic figures in a benign endometrium could become very significant.

A survey of the literature indicates a division of opinion regarding the probable presence of active estrogenic ovarian tumors in postmenopausal women with vaginal hemorrhage without palpable adnexal masses. Arguments concerning the importance of a palpable pelvic tumor, of the type of endometrium, and of an adequate duration of the postmenopausal amenorrhea have been carried on extensively in the literature. In 1925, Meyer[1] urged the consideration of an estrogenic ovarian tumor in a postmenopausal woman with vaginal bleeding and hypertrophy of the endometrium even though no mass could be felt on pelvic examination. Other authors in agreement with Meyer were Treite and von Pallos,[2] who stated firmly that vaginal bleeding following 2 years of postmenopausal amenorrhea in a patient with endometrial hyperplasia but without a palpable pelvic tumor suggested the presence of an estrogenic ovarian tumor, but if a 6 year period of postmenopausal amenorrhea had elapsed, an exploratory laparotomy was demanded.

On the other hand, Benthin,[3] Fahmy,[4] Breipohl,[5] Taylor and Millen,[6] Falls and associates,[7] and Dhom[8] denied the significance of either vaginal bleeding or endometrial hyperplasia as a sign of an estrogenic ovarian tumor in a postmenopausal woman. It is interesting that Novak and Brawner[9] in 1934 were willing to consider the presence of an estrogenic ovarian tumor in a postmenopausal woman with vaginal bleeding and endometrial hyperplasia but in 1936 and in subsequent years, Novak and his co-workers[10] reversed this opinion and continued thereafter to state that a palpable pelvic tumor was necessary before an exploratory laparotomy could be advised. It should be added, however, that these negative conclusions are to some degree vitiated by the failure of many of the authors quoted above to examine the ovaries of the women studied.

A further and more fundamental explanation of this division of opinion is probably due to the neglect in appreciating the value of the benign endometrial mitotic figure as an indicator of estrogenic activity, once administered estrogen has been ruled out. Most of the evidence upon which the presence of estrogen activity has been postulated in the literature consists of histologic details which are found in hyperplasia or cystic hyperplasia of the endometrium. These details, all of which were found in the endometria in the cases herein presented, are tall epithelial cells, pseudostratification of the epithelial cells, cellularity of the stroma without fibrosis, plump chromatin-rich nuclei in both epithelial and stromal cells, cystic dilatation of glands, gross thickness of the endometrium, polypoid configuration and branching of the glands. It must be pointed out, however, that, without mitotic figures, these details merely mean that estrogenic activity had occurred but that it was not necessarily concurrent. The only definite histologic indication of concurrent estrogen activity is the benign endometrial mitotic figure.

As an illustration of this neglect, reference may be made to Kottmeier's[11] use of the term hyperproliferative in cases of estrogenic ovarian tumors in which he noted the occasional lack of mitotic figures and concluded that the presence of mitotic figures was not essential for the diagnosis of an active estrogen influence on the endometrium. Other authors like Fahmy[4] did not define hyperplasia of the endometrium so that one is at a loss to know whether mitotic figures were present in the endometrium in their cases.

Another factor lending confusion to the problem is the persistence of hyperplasia of the endometrium in the postmenopausal period in women who have undergone anovulatory menopausal activity in the absence of estrogen-secreting ovarian tumors or thecomatosis. This persistence, which was recognized by Taylor and Millen[6] and Novak and Novak,[12] eventually results in regressive changes such as complete epithelial atrophy and stromal fibrosis, but these regressive changes cannot be used to exclude the presence or absence of estrogenic lesions in the ovary in view of the inability of the endometrium to respond indefinitely to continuous estrogen stimulation. An example of this is afforded by the endometria with hyperplasia induced by administered estrogen. I observed such a case in which a 66-year-old postmenopausal woman without estrogenic ovarian tumors or thecomatosis had been receiving daily 1.25 mg. of Premarin for 8 years. The endometrium displayed a marked cystic hyperplasia with both cellular and fibrotic stroma but no mitotic figures.

Thecomatosis.—The inclusion of the thecomatosis of Case 6 in the group of nonpalpable estrogenic ovarian tumors is made on the basis of similar endocrinologic, diagnostic, and therapeutic considerations. Intermittent vaginal hemorrhages of 3 months' duration in a woman of 64 with a postmenopausal amenorrhea of 10 years, together with a negative pelvic examination and mitotic figures in a benign endometrium indicative of estrogen activity, are precisely the findings to be expected in the cases of nonpalpable estrogenic ovarian tumors. No masculinization was observed.

The term thecomatosis is used as suggested by Woll and associates,[13] who included this type of ovarian lesion under the heading of cortical stromal hyperplasia but did not correlate the presence of this lesion with the type of benign endometrium present. They did note a high incidence of endometrial cancer in their cases of thecomatosis and attributed estrogen secretion to the theca cells. A peculiar diffuse cell proliferation derived presumably from the stromal cells is seen in thecomatosis, resulting in the appearance of cells possessing epithelioid characteristics with abundant acidophilic cytoplasm, occasionally vacuolated and round to oval vesicular nuclei containing small but prominent nucleoli. The cytoplasm may contain lipoid and pigment. At present, the designation of these cells as theca or luteinized theca cells has superseded that of interstitial cells but it must be understood that the term theca is based on inference. The difference histopathologically between thecomatosis and thecomas is that the cells in the former are diffusely distributed rather than collected in circumscribed tumors. A further obstacle to a clear understanding of the nature of these cells is the fact that similar cells are seen in the ovarian cortical stroma in cases of masculinization resembling very much that found in the Stein-Leventhal syndrome, to which the term hyperthecosis or diffuse luteinization of the ovaries has been applied. There is present, then, the peculiar situation where morphologically similar cells produce either estrogen[13] or androgen.[14] An attempt at differentiation of the two types of theca cells was made by Laffargue and Luscan[15] who stated that the androgenic theca cells contain Reinke crystalloids thus bringing them into some sort of relationship with the ovarian hilar and the testicular interstitial cells. My personal observation,

however, failed to disclose these crystalloids in a typical case of hyperthecosis with hypertrichosis and clitoridauxe. Perhaps it would be preferable to employ the terms estrogenic thecomatosis and androgenic hyperthecosis.

As for the anomalous situation in which cells morphologically alike can secrete either estrogen or androgen, one must consider the adrenal cortical tumors where it has been established that morphologic similarity may be consistent with varied endocrinologic activity. According to Karsner[16] it is impossible to tell from the appearance of the cells of the adrenal cortical tumors what type of hormone is being produced.

Recently a new note of contention has been introduced by Roddick and Greene,[17] who have attempted to discount the significance of ovarian cortical stromal hyperplasia as an estrogen-producing factor and have discussed theca-cell proliferation under the heading of stromal hyperplasia. It is interesting that they found 15 cases of theca-cell proliferation with atrophic or inactive hyperplasia of the endometrium without mitotic figures and in only one case with apparently the same type of cell proliferation were mitotic figures present in the endometrium. The obvious explanation, although no mention of masculinization was made by these authors, is that in their cases of apparent diffuse theca-cell proliferation with atrophic endometrium, the ovaries do not contain endocrinologically inactive theca cells but rather theca cells producing androgen, so that their findings in no way preclude the possibility of estrogen-producing theca cells.

In this connection, it is interesting that the literature contains far more cases of androgenic hyperthecosis than estrogenic thecomatosis, which is in keeping with the relative proportions of the two types of cells in the cases of Roddick and Greene. Only 2 cases of estrogenic thecomatosis reported as such could be found in the literature, one of Laffargue and Luscan[15] and the other of Bourg.[18] As an example of the numerical superiority of androgenic hyperthecosis, the articles by Shippel,[14] Plate,[19] Geist and Gaines,[20] Rottino and McGrath,[21] and Bergstrand[22] may be cited. This disproportion is all the more striking in view of the predominance of estrogen-producing thecomas which, of course, are also presumably composed of thecal cells. In fact, McKay and coworkers[23] contend that only theca cells produce estrogen in the mixed theca- and granulosa-cell tumors as well as in the ostensibly morphologically pure granulosa-cell tumor.

Finally, one must consider other possible sources of endogenous estrogen in the postmenopausal women and their ability to produce mitotic figures in the benign endometrium. The two most likely possibilities are the adrenal cortex and the hyperplastic ovarian cortex. Evidence for the adrenal secretion of estrogen lies in such studies as that of Mack[24] on the glycogen index in postmenopausal and castrated women based on vaginal smears. McBride's[25] study of estrogen excreted in the urine of postmenopausal and castrated women also suggests the possibility of the adrenal as a source of estrogen. Another significant item indicative of estrogen production by the adrenal is the presence of estrogen-producing cortical adenomas in that organ.[16] Despite all these indications that the adrenal is a source of estrogen, it is extremely doubtful that the adrenal at any time secretes enough estrogen to produce mitotic figures in the benign, perhaps hyperplastic endometrium. In fact, Woll and his associates[13] were unable to find any evidence that the adrenal can cause proliferative changes in the endometrium. As for the hyperplastic ovarian cortex, Roddick and Greene[17] doubt that it can excrete estrogen, much less cause proliferative changes in the postmenopausal endometrium.

Personal experience as well as a perusal of the literature indicates clearly that women with colporrhagia after more than 3 years of postmenopausal amenorrhea and with a benign hyperplastic endometrium containing mitotic figures

with or without a palpable pelvic tumor are very likely to harbor a thecoma, a mixed granulosa- and theca-cell tumor, or estrogenic thecomatosis, and deserve an exploratory laparotomy.

Lesions of the fundus and cervix of the uterus and administered estrogen must be ruled out. The presence of hyperplasia of the endometrium without mitotic figures cannot be considered proof that concurrent estrogen activity is present and need not indicate the presence of an estrogenic lesion in the ovaries.

Summary

In 6 women of 60 years of age or over with vaginal bleeding, 2 cases of thecoma, 3 cases of mixed granulosa- and theca-cell tumor, and one case of estrogenic thecomatosis were found. Except for one woman with a postmenopausal period of amenorrhea of 2 years, the others had postmenopausal periods of 10 years or longer. No palpable adnexal masses were felt in 4 of these 6 women but all had hyperplasia of the endometrium with mitotic figures. The importance of mitotic figures as an indicator of estrogenic activity in the endometrium is stressed. It is recommended that any colporrhagic woman with a postmenopausal amenorrhea of more than 3 years and hyperplasia of the endometrium with mitotic figures should have an exploratory laparotomy whether or not a palpable adnexal mass is present, provided no estrogen has been administered. The use of the terms estrogenic thecomatosis and androgenic hyperthecosis is suggested to lessen the confusion due to morphologically similar cells producing different hormones.

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MALIGNANT LYMPHOMA INVOLVING THE OVARIES

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ALTHOUGH there is a dearth of references to ovarian involvement in malignant lymphoma, occasional clinical instances are encountered. Since the entity is so unusual, we felt it worth while to report 6 cases of ovarian lymphoma which were encountered at our institution over the past 20 years and in which pelvic symptoms or signs necessitated laparotomy.

Since Kundrat's[8] classic article in 1893 on lymphosarcoma with primary origin in various tissues and organs, there have been surprisingly few case reports of clinically significant lymphomatous involvement of the ovary. We found only 4 cases in which the lesion was designated a primary ovarian lymphoma[2, 16, 19, 20] (Table I); in the remaining 24 cases the ovarian involvement was considered to be secondary.[1, 3, 5, 6, 9, 10, 12, 13, 15, 17-19] This might give the impression that ovarian involvement with malignant lymphoma is extremely rare. Johnson and Soule,[7] however, in a review of necropsy records found secondary ovarian involvement of some degree in 10 of 43 females who died of malignant lymphoma at the Mayo Clinic over an 8 year period. None of these patients presented gynecologic symptoms or exhibited unusual gynecologic signs while living. Lucia and co-workers[11] have also reported from necropsy studies that 2 of 11 females with malignant lymphomas had ovarian involvement.

TABLE I. REPORTED CASES OF "PRIMARY" OVARIAN LYMPHOMA*

AUTHOR	YEAR	AGE OF PATIENT	PRESENTING SYMPTOM	SURVIVAL PERIOD
Walther[19]	1934	54	Vaginal bleeding	5 months
Durfee and associates[2]	1937	23	Loss of strength	12 days
Sugarbaker and Craver[16]	1940	Not stated	Not stated	Not stated
Zeigerman and associates[20]	1956	36	"Fibroids"	9 months

*The microscopic diagnosis was "lymphosarcoma" in each case.

*The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

Primary extranodal genesis of malignant lymphoma is uncommon, and it occurs most frequently in locations such as the gastrointestinal tract[4] which normally exhibit aggregates of lymphocytes. Such aggregates are never found in the normal ovary, although they may occur in association with the ovarian lesions of chronic pelvic inflammatory disease.[19] Lymphocytic foci in preexisting ovarian teratomas[2] represent another possible source for the development of primary malignant lymphomas.

What should we accept as a case of primary ovarian malignant lymphoma? The word "primary" implies one origin only, with secondary metastatic lesions. Whether this can be proved in the 4 reported ovarian cases is open to question, even though we accept the present-day concept of malignant lymphoma as being sometimes of multicentric origin. So perhaps it would be best to consider the ovaries as one of several sites involved. Durfee and coworkers[2] considered the tumor in their case as being primary in the ovary simply because it was the largest mass present, although many other intra-abdominal organs were also involved. Walther,[19] in reporting his "primary" cases, stated that the retroperitoneal nodes were minimally "enlarged" at the time of laparotomy which was performed for a large left ovarian tumor. The case of Sugarbaker and Craver[16] is only mentioned and no details are reported. The patient with "primary" ovarian lymphosarcoma reported on by Zeigerman and co-workers[20] died 9 months postoperatively with abdominal lymphosarcomatosis, in spite of no apparent gross lesions other than those involving the ovaries at the time of laparotomy. We agree with Zeigerman and his co-workers that the terms "primary" and "secondary" are misleading in a discussion of lymphomas of the genital tract. The important point is simply to keep in mind that malignant lymphoma can present in rather unusual ways when the female genitals are involved.

The reported instances of obviously secondary ovarian involvement seem to have arisen, for the most part, from lesions located in the gastrointestinal tract, usually in the small intestine and stomach. Spread to the ovary from these "primaries" is considered to be chiefly by a "seeding" process like that observed with Krukenberg tumors. Muscatello[13] emphasized this direct transperitoneal spread in spite of the fact that many ovarian vessels in his patient contained thrombi of lymphoblasts. Invasion of the ovaries by retrograde flow via the lymphatics is also considered possible. Rouvière and Valette[14] many years ago demonstrated retroperitoneal lymphatic drainage from the bowel into the lumbar group of nodes, into which also drain the ovarian lymphatics. Finally, it is conceivable that the "secondary" ovarian lymphomas may have arisen simultaneously from cells trapped in the ovary. This further emphasizes the futility of attempting to sort the cases into secondary and primary categories.

The subclassification of malignant lymphomas utilized at the Mayo Clinic is: reticulum-cell sarcoma, lymphosarcoma (lymphocytic and lymphoblastic types), Hodgkin's disease, and giant follicular lymphoma. This subclassification will be used in the following case reports.

CASE 1.—A 58-year-old postmenopausal, married, white woman, gravida ii, para ii, came to the clinic on Dec. 1, 1948, complaining of weakness of one year's duration. She had also had a moderate loss of weight associated with anorexia and constipation. Her abdomen had been "swollen" for 2 months.

Fig. 1.—Case 1. Solid, lobulated ovaries showing bilateral metastatic lymphoblastomatosis.

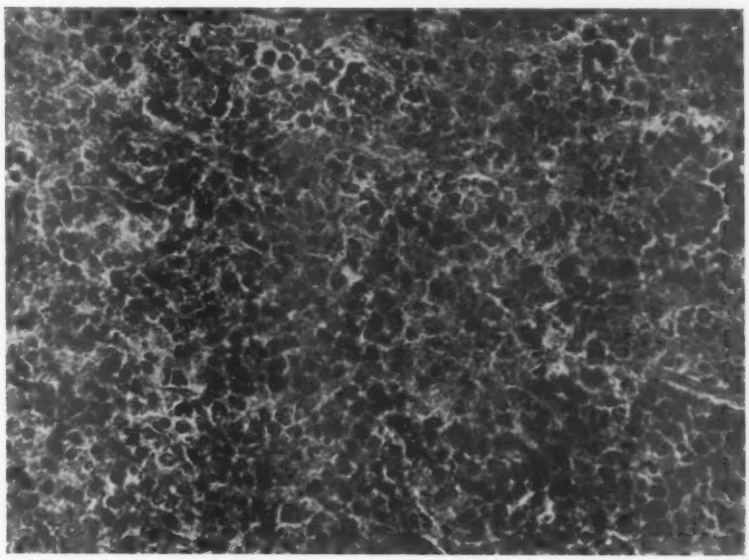

Fig. 2.—Case 1. Ovarian stroma is completely replaced by dark, round, malignant cells of the lymphoid series. (Hematoxylin and eosin; ×350.)

On examination the patient was moderately emaciated and appeared chronically ill. She weighed 118 pounds and her temperature was normal. There was severe dorsal kyphoscoliosis. Several small inguinal lymph nodes were palpable. The abdomen was markedly distended and a fluid wave could be elicited. The entire right lower quadrant was filled with a hard nodular mass. Pelvic examination following removal of 3,750 c.c. of cloudy straw-colored fluid by paracentesis revealed a hard mass that seemed to be arising from the right adnexal region. This mass filled the cul-de-sac and was pressing on

the vagina and the cervix. No malignant cells were demonstrated in the paracentesis fluid. Results of laboratory tests were negative except for an erythrocyte sedimentation rate of 111 mm. in 1 hour (Westergren).

At laparotomy on Dec. 6, 1948, the liver and stomach were normal to palpation. The spleen was approximately twice normal size. One portion of the mesentery of the ileum was nodular and grayish. Both ovaries were greatly enlarged, particularly the right which was attached to the mesentery of the small bowel and the ascending colon. Bilateral salpingo-oophorectomy was done. The patient died on Dec. 17, 1948.

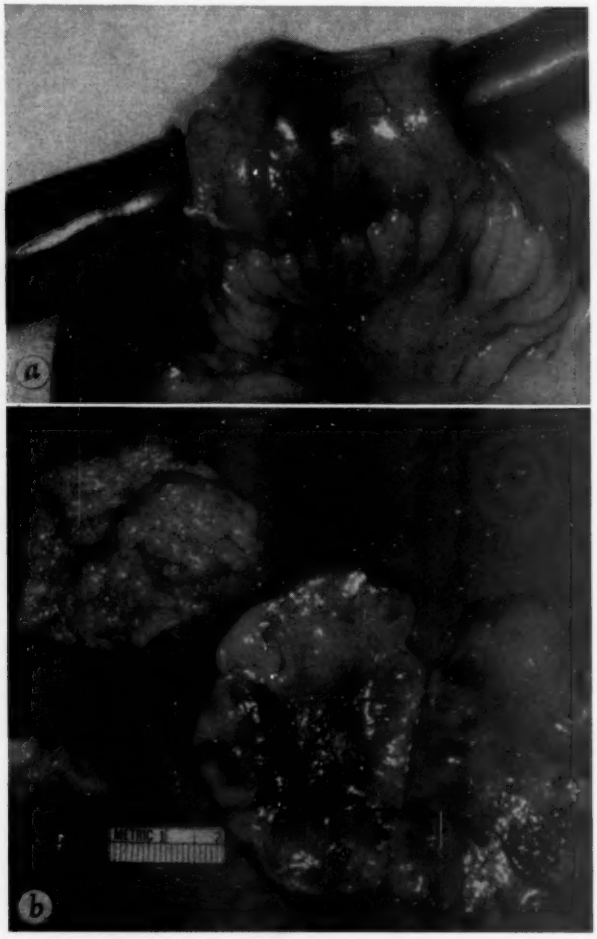

Fig. 3.—Case 2. *a*, Annular primary reticulum cell sarcoma of the jejunum showing features of intussusception. *b*, Metastatic ovarian lesion shows symmetric expansion of the ovary by a solid hemorrhagic tumor.

Necropsy showed abdominal lymphosarcomatosis. Grossly, both ovaries were somewhat symmetrically enlarged and solid (Fig. 1). The right measured 14 by 20 by 12 cm. and weighed 1,600 grams. As mentioned previously, it exhibited some surface adhesions. The left ovary, completely free from such adhesions, measured 20 by 6 by 6 cm. and weighed 800 grams. All surfaces had a homogeneous grayish-yellow appearance and a completely solid consistency. Lacking were the central zones of cyst formation and necrosis so commonly observed in primary solid ovarian carcinoma. The tumors were less firm and fibrous, however, than the typical examples of metastatic fibrocarcinomas of the Krukenberg type that we have observed in cases in which the primary lesion was in the stomach.

Microscopically, no identifiable ovarian tissue was discerned. Both masses consisted of sheets of small, uniform, dark-staining round cells in which the nuclei occupied more than 90 per cent of the cell volume (Fig. 2). Chromatin was so dense that it was not always possible to delineate the macronucleoli that were present, usually as single dark-staining masses, within each nucleus. Actually, no interstitial elements were present between the tumor cells.

In certain areas, probably as a result of tumor cells outstripping their blood supply, wide zones of necrosis were present in which only the ghostlike remains of original cells were discernible. Hemorrhage was sometimes present in these areas.

The diagnosis of the ovarian lesions was metastatic lymphoblastic lymphosarcoma.

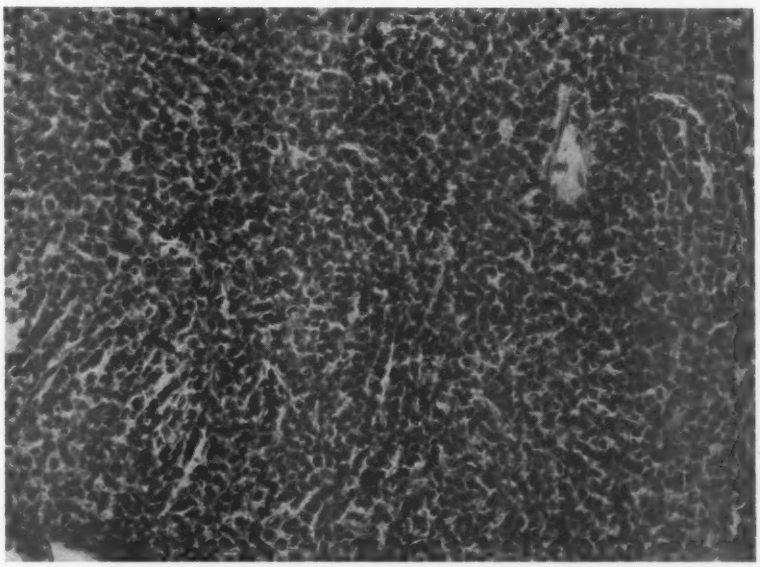

Fig. 4.—Case 2. Metastatic ovarian lesion showing "single filing" which under most other circumstances is characteristic of metastatic scirrhous adenocarcinoma. (Hematoxylin and eosin; ×200.)

CASE 2.—A 27-year-old parous white woman came to the clinic on Aug. 3, 1953, because of intractable low back pain of 2 weeks' duration. Her weight had decreased from 200 to 170 pounds in the past 5 months. Her menstrual history was normal.

On physical examination small nodes were palpable in the left axilla. Pelvic examination revealed a firm, egg-sized, somewhat movable mass in the right lower quadrant over the right common iliac region. Hyperextension and forward flexion of the spinal column caused pain in the right lumbosacral region. Straight-leg raising was painful on the right after an angle of 45 degrees was reached, but was possible to 90 degrees. The results of neurological examination were otherwise negative.

The results of urinalysis were negative. The hemoglobin content was 11.9 Gm. per 100 c.c. of blood, and the erythrocyte count was 4.18 million and the leukocyte count 7,100 per cubic millimeter. The differential count was: lymphocytes 20 per cent, monocytes 5 per cent, segmented neutrophils 16 per cent, band forms of neutrophils 47 per cent, metamyelocytes 5 per cent, and late myelocytes 7 per cent. The blood smear revealed increased rouleau formation and considerable myeloid immaturity in several stem cells. The platelets seemed adequate. The erythrocyte sedimentation rate was 94 mm. in 1 hour. Roentgenograms of the entire spinal column and thorax presented normal findings. Excretory and retrograde urograms of the right ureter and kidney gave normal findings. The cerebrospinal fluid also was normal.

At operation the abdomen contained a small amount of cloudy fluid suggestive of chylous ascites. The uterus was normal sized, but both ovaries were enlarged and soft. An annular mass, 5 cm. in length, was found in the lower part of the jejunum the residual lumen of which was just large enough for passage of a finger (Fig. 3, *a*). There were large nodes in the adjacent mesentery. The liver, stomach, gall bladder, kidneys, and retroperitoneal tissues were normal. The spleen was of normal size and consistency. The omentum was granular and contracted. Right oophorectomy was done and biopsy specimens were taken from the left ovary and from the omentum.

Postoperatively, the patient was given deep roentgen therapy to the lumbar region with much relief of her back pain. A bone-marrow study showed marked increase in immature lymphocytes of sufficient number and of sufficient degree of immaturity to suggest acute or subacute lymphatic leukemia. This patient died at home on Aug. 26, 1953, 23 days after registering at the clinic.

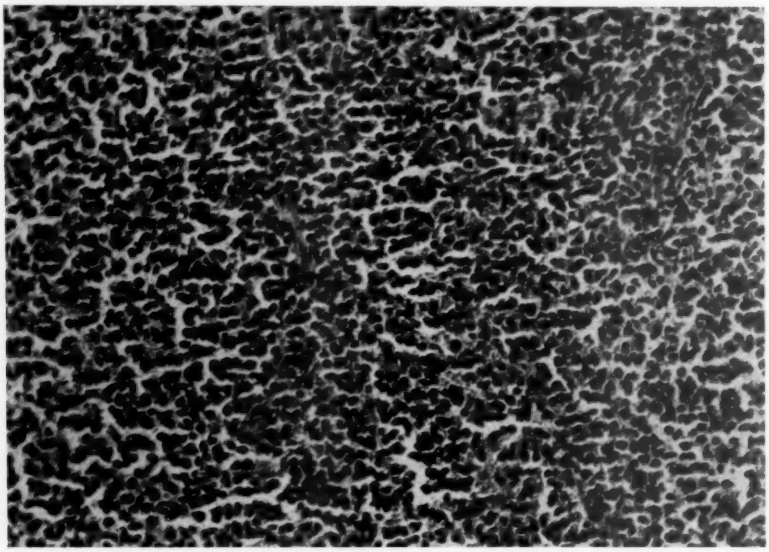

Fig. 5.—Case 3. Section from the right ovary which was lobulated, solid, and 5.5 cm. in diameter. The stromal architecture is completely obliterated by the massive infiltration of lymphoblasts. (Hematoxylin and eosin; ×200.)

Grossly, the removed ovary was symmetrically enlarged, measuring 5 by 3 by 3 cm. (Fig. 3, *b*). On cut surface there was absence of the usually expected landmarks such as corpora albicantia, follicles, and corpora lutea. Instead, the bulging cut surfaces were homogeneously gray from replacement by tumor tissue.

Microscopically, as in Case 1, there was replacement of identifiable ovarian stroma by a dense infiltrate of small and large round cells. In some zones the smaller elements predominated and in these zones a peculiar arrangement of cells in single file (Fig. 4) was reminiscent of scirrhous carcinoma. This phenomenon of "single filing" is not infrequently observed in instances wherein a malignant lymphoma invades solid structures like dense ovarian stroma.

In other zones there appeared to be an admixture of small dark cells with larger and paler cells showing relatively larger amounts of cytoplasm and uniform nuclei. These were regarded as malignant reticulum cells and the tumor accordingly was classified as a mixed lymphoma. The microscopic picture presented in the left ovarian and omental specimens was similar to that described for the right ovary. "Single filing" of cells was not observed in the omental specimen, however.

CASE 3.—A single, 54-year-old white woman was referred to the clinic on Jan. 11, 1954, by her home physician because of a history of "swollen neck glands" of 7 months' duration. Her last menses had occurred in 1941, at age 41, when subtotal hysterectomy had been performed by her home physician for "tumors."

Physical examination revealed a healthy-appearing woman. Her temperature was 99° F. and she weighed 168 pounds. Firm, nontender, symmetric submaxillary nodules were palpable, measuring from 2.5 to 4 cm. in diameter. A right adnexal mass 6 to 7 cm. in diameter and a questionable smaller left adnexal mass were noted on pelvic examination. Laboratory findings including hemoglobin determination, erythrocyte count, leukocyte count, and differential count were all within normal limits. Mild anisocytosis was evident on the blood smear. A roentgenogram of the thorax was interpreted as showing no abnormality. A cervical smear proved negative for malignant cells. There was Grade 1 albuminuria.

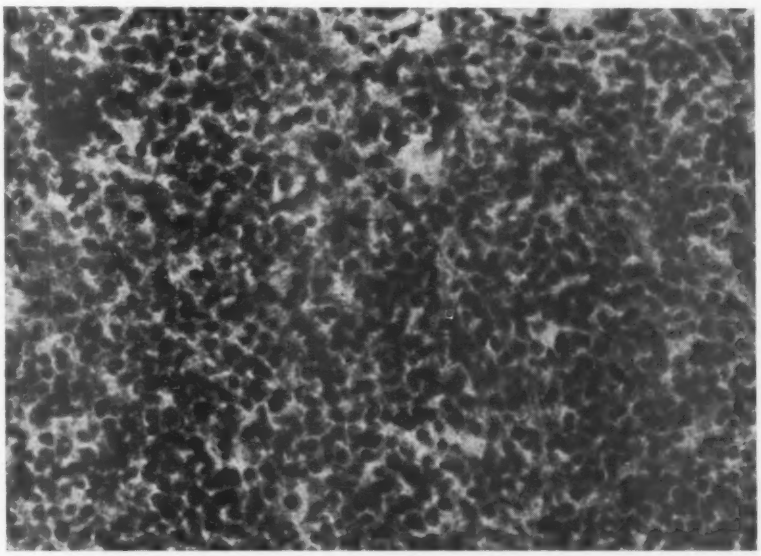

Fig. 6.—Case 4. Section from the left ovary in a case of mediastinal lymphoblastoma with bilateral ovarian metastasis. (Hematoxylin and eosin; ×300.)

Because of the adnexal masses, the abdomen was explored on Jan. 15, 1954, and biopsy of the submaxillary glands was planned for the postoperative period. Laparotomy revealed a spleen enlarged approximately three times normal size. The liver, stomach, duodenum, gall bladder, and pancreas were normal to palpation. There was considerable thickening in the retroperitoneal region around the root of the mesentery of the small bowel, and multiple nodules were easily palpable over the entire anterior visceral peritoneum. A hard, firm, nodular mass involved the right ovary; this was removed along with several peritoneal nodules.

The right ovary weighed 39 grams, and measured 4.5 by 5.5 by 3.5 cm. It exhibited gross features similar to those detailed in Case 1. Microscopically it showed metastatic lymphoblastic lymphosarcoma (Fig. 5) as did the peritoneal nodule. On Jan. 20, 1954, biopsy of the left submaxillary gland disclosed lymphoblastoma.

Postoperatively the patient received roentgen therapy to the abdomen and neck. Further roentgen therapy to various portions of the body was given in April, 1954, September, 1954, March and September, 1955, and February and September, 1956. As of September, 1957, her peripheral blood counts were normal and she had no systemic manifestations of her disease. The concentration of blood urea was 32 mg. per 100 c.c. and the hemoglobin content was 11.4 Gm. per 100 c.c. The erythrocyte sedimentation rate was 37 mm. in 1 hour. She was given additional roentgen therapy to enlarged nodes in the neck and scalp.

CASE 4.—A 36-year-old, gravida iv, para ii, white woman was admitted to the clinic on May 21, 1944, upon referral from her home physician. In November, 1943, she had received roentgen treatment for a mediastinal tumor and the response had been good. In January, 1944, pain had developed in the pelvis, and in February her menstrual flow was extremely heavy and 10 days late. Pelvic examination at that time revealed a "pelvic tumor," and on February 20, subtotal hysterectomy and bilateral salpingo-oophorectomy were performed (elsewhere). The microscopic diagnosis at that time was primary medullary carcinoma of the ovaries (bilateral), and it was thought that the mediastinal mass had been secondary to the ovarian carcinoma.

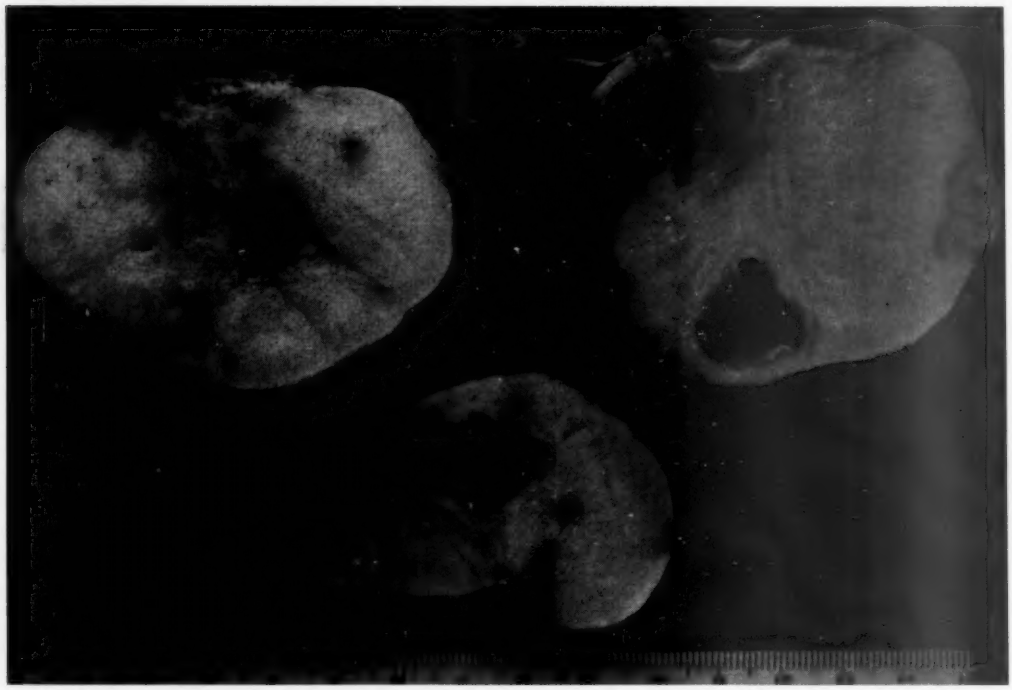

Fig. 7.—Case 5. Sections of both ovaries showing metastatic lesions from primary mediastinal lymphoblastoma. Tumors predominantly solid.

Grossly the left ovary was said to have measured 6.5 by 3.5 by 3 cm. and to have had a firm capsule. Cross section had showed a rather soft, pinkish tumor with a number of tiny follicular cysts beneath the surface. The right ovary measured 3 by 3 by 1.5 cm. and was similar in gross characteristics to the left. Metastatic lesions had subsequently developed in various osseous sites, the lung, and the skin. Roentgen therapy had been given to the pelvis for treatment of the osseous lesions.

The physical examination at the clinic showed a thin, chronically ill white woman. Her temperature was 99° F. Except for increased vocal fremitus in the apex of the right lung, physical examination gave essentially negative results. The hemoglobin content was 8.1 Gm., the leukocyte count 3,700, and the erythrocyte sedimentation rate 137 mm. in 1 hour. X-ray study revealed lesions that were consistent with a diagnosis of malignant disease in both femurs and in the ilium. The thoracic roentgenogram showed a circumscribed mass 7 cm. in diameter in the left lung.

The original tissue sections of the ovaries were obtained from the referring physician and his microscopic diagnosis of lymphosarcoma was confirmed (Fig. 6). The type was lymphoblastic with all areas of ovarian tissue obscured by areas of small lymphoblasts. Here and there the phenomenon of "single filing" was again apparent.

The patient was referred back to her home physician for further roentgen therapy. She died on Dec. 13, 1944.

CASE 5.—A 30-year-old nulligravid married white woman was admitted to the clinic on June 10, 1937. Six months previously a mediastinal mass had been discovered by her home physician. Irradiation therapy was given with complete relief of symptoms and a resultant decrease in the size of the mass. In March, laparotomy had been performed by her home physician because of severe lower abdominal pain and the finding of "pelvic tumors" on examination. Two orange-sized ovarian masses were removed which were diagnosed as lymphosarcoma. Postoperative irradiation therapy to the pelvis was given; she had had no menses subsequently. Further irradiation therapy had since been given on two occasions for thoracic pain, but without relief.

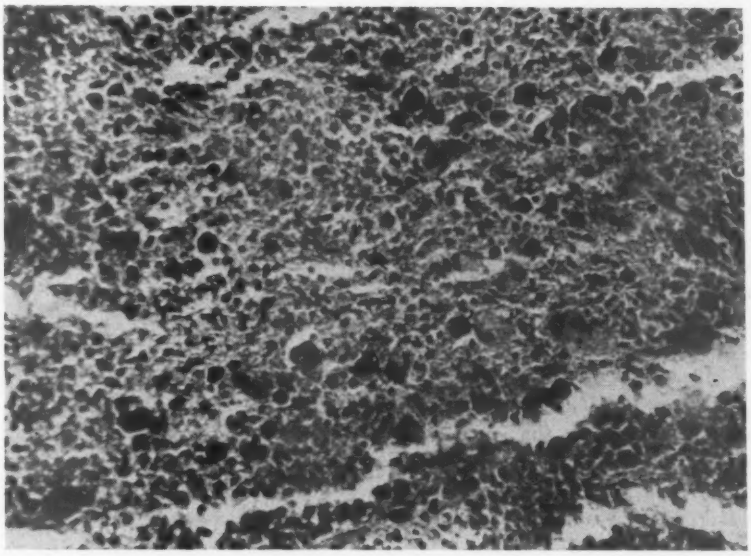

Fig. 8.—Case 6. Microscopic section of right ovary in Hodgkin's disease involving the mediastinum and cervical nodes. Numerous Reed-Sternberg cells are apparent. (Hematoxylin and eosin; ×200.)

Her chief complaint on admission to the clinic was severe substernal pain. There had been no loss of weight. Physical examination revealed a surprisingly well-nourished, pale white woman. Her temperature was 98.6° F. and her pulse rate 76 per minute. The submaxillary salivary nodes were enlarged, and one hard, fixed, left supraclavicular node was palpable. Results of the remainder of the general examination including pelvic examination were negative.

Laboratory findings included a hemoglobin content of 13.1 Gm. and an erythrocyte count of 3.88 million. The leukocyte count was 6,850 with the following differential: lymphocytes 75 per cent, monocytes 13.5 per cent, neutrophils 7.6 per cent, eosinophils 2.5 per cent, and basophils 0.5 per cent. The blood smear was normal. Roentgenograms of the thorax did not disclose any abnormality.

After the tissue sections from the ovaries had been reviewed at the clinic and a diagnosis of lymphoblastic lymphosarcoma confirmed, the patient was sent home for further palliative x-ray therapy as needed. She died 3 months later. As described by the home pathologist the two ovarian masses measured 6.5 by 6 cm. and 6 by 3.5 cm., respectively, and were of a yellowish hue (Fig. 7). Cut section revealed white, brainlike tissue.

CASE 6.—A 19-year-old married woman, gravida i, para i, was first seen at the clinic on April 24, 1954, complaining of fatigue and weight loss of 7 months' duration. Her past

history disclosed that appendectomy and right oophorectomy had been done at age 15, but the ovarian diagnosis was unknown to the patient. At age 17, a mediastinal tumor had been removed and the patient stated it was diagnosed "teratoma." Six months prior to her admission to the clinic, cervical adenopathy developed and local excisions of nodes had been done twice with the diagnosis of "inflammatory tissue." She had recently noticed a tender mass in the abdomen. Thoracic roentgenograms taken by her home physician were said to reveal a mediastinal mass. She had lost 14 pounds in the past 6 months and had experienced low-grade fever over most of the same period. Her menstrual history was essentially normal.

Physical examination showed the temperature to be 99° F. There were enlarged, matted, left postcervical nodes and one large left anterior cervical node. Nodes also were palpable in the left supraclavicular region and the left axilla. The spleen was easily felt, and a large mass palpated in the epigastrium was thought to represent the left lobe of the liver. The remainder of the physical examination gave essentially negative results.

The leukocyte count was 17,600 with a differential count as follows: neutrophils 79 per cent, lymphocytes 10 per cent, monocytes 10.5 per cent, and eosinophils 0.5 per cent. The blood smear showed increased rouleau formation, occasional polychromasia, and mild hypochromasia. The platelets were adequate. The hemoglobin content was 10.4 Gm. The erythrocyte sedimentation rate was 55 mm. in 1 hour. The direct reaction for serum bilirubin was negative, and the indirect reaction gave a value of 0.46 mg. per 100 c.c. of serum. Total serum proteins measured 7.05 Gm. per 100 c.c., with a normal albumin-globulin ratio. A mediastinal mass and numerous nodular densities in the bases of the right and left lungs were seen on roentgenograms of the thorax. X-ray studies of the upper part of the gastrointestinal tract with the aid of barium gave normal results.

In sections from tissue removed at previous surgical procedures the right ovary featured a marked proliferation of lymphocytes and reticulum cells. Many of the latter appeared to be of giant dimensions, with lobulated nuclei and multinucleated forms typical of Reed-Sternberg cells (Fig. 8). Zones of fibrosis were scattered about, and eosinophils were present in small clusters throughout the sections studied. Our diagnosis was malignant lymphoma, Hodgkin's type. The pathologist who studied the mediastinal mass that had been removed previously stated that some parts of that tumor resembled Hodgkin's disease but that the final diagnosis had been anterior mediastinal cystic benign tumor, unclassified.

The final diagnosis was widespread Hodgkin's disease with ovarian involvement. Further therapy with roentgen rays and with nitrogen mustard was advised. The patient elected to receive this treatment at home.

Summary

From a review of the literature pertaining to ovarian malignant lymphoma, 4 cases of so-called primary and 24 cases of obviously secondary or "metastatic" disease are cited. In addition, 6 personally studied cases are presented in which clinical features pointed to ovarian participation in a more generalized lymphoblastomatous process.

The grim prognosis associated with unilateral or bilateral ovarian tumors of this type, regardless of size, raises questions regarding the validity of the notion that malignant lymphoma is ever a primary process in these organs.

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MALIGNANT BRENNER TUMOR OF THE OVARY

With the Report of One Case

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TO PRESENT a report of a malignant Brenner tumor of the ovary in the face of diversified opinion as to the diagnosis may at first glance seem presumptuous. There has ever been difficulty, however, in obtaining a unanimous opinion from pathologists with reference to many malignant ovarian tumors. The multiplicity of such opinions results, in all probability, from the divergence of interpretation of the histogenesis of these growths. No one has as yet brought forth a classification of ovarian neoplasms that has met or is likely to meet with the approval of all those interested in the subject. The tumor and the case history herein presented were subject to the same confusion.

The patient, an 84-year-old white woman, a widow, whose menopause had been at the age of 52 years, had had 7 pregnancies and delivered 7 full-term babies with no known complications.

In February, 1955, the patient entered the hospital for a diagnostic dilatation and curettage because of uterine bleeding. The pathologic report noted: "a number of fair-sized fragments of endometrium of a polypoid nature and composed of cystic glands. The endometrial stroma is atrophic." We were unable to demonstrate any gross or microscopic lesions of the uterus by way of direct intracavitary examination and with repeated Papanicolaou smears, which were negative.

In January, 1956, she re-entered the hospital because she had recently noted progressive enlargement of the lower abdomen associated with pressure symptoms in the pelvis, and slight blood-tinged secretion from the uterus. There had been no breast changes.

The preoperative findings were as follows: The scar of a former vulvectomy for diffuse leukoplakia, performed April 27, 1953, was noted. The pathologic report had been kraurosis vulvae with leukoplakia. The cervix was normal. The body of the uterus was slightly and symmetrically enlarged, which, in a patient 84 years old, was quite noticeable. A large cystic ovarian mass, free and movable, was present.

On Feb. 1, 1956, a left salpingo-oophorectomy with removal of the tumor and direct intracavitary uterine curettage via an incision through the midline of the anterior fundus were performed. The tumor, arising from the left ovary, was partially cystic and partially solid, and occupied an area well past the midline, extending to the umbilicus. The cystic mass presented a solid island in the anterior area. The capsule was intact and free of adhesions.

Fig. 1.—Photomicrograph showing the cellular arrangement of a portion of the tumor presenting typical malignant change and associated with cell nests.

Fig. 2.—Photomicrograph showing by low magnification the rather typical Brenner cell arrangement in a less malignant area. The extreme cellularity and anaplasia strongly suggest malignant change.

Fig. 3.—High-power photomicrograph showing typical epithelial nests with early degenerative changes and anaplasia.

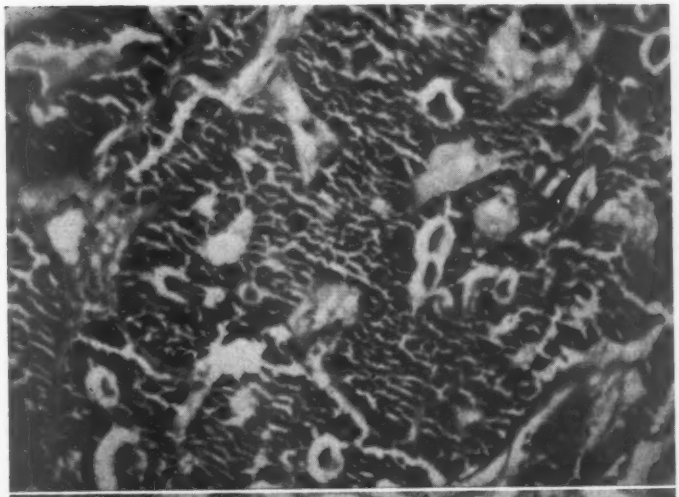

Fig. 1.

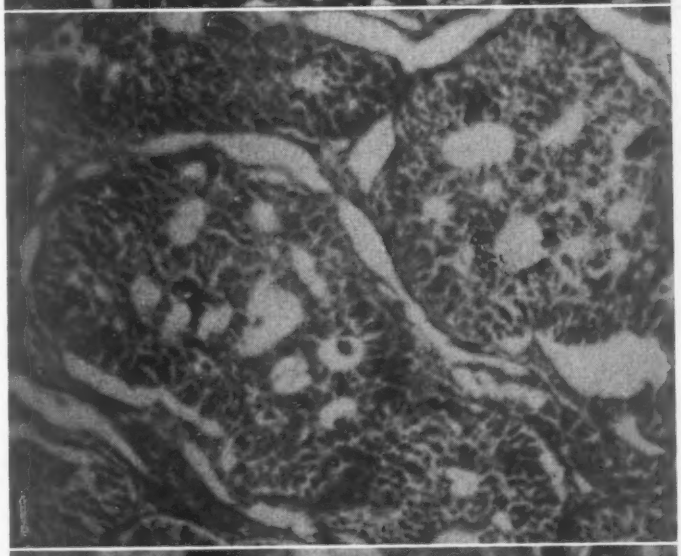

Fig. 2.

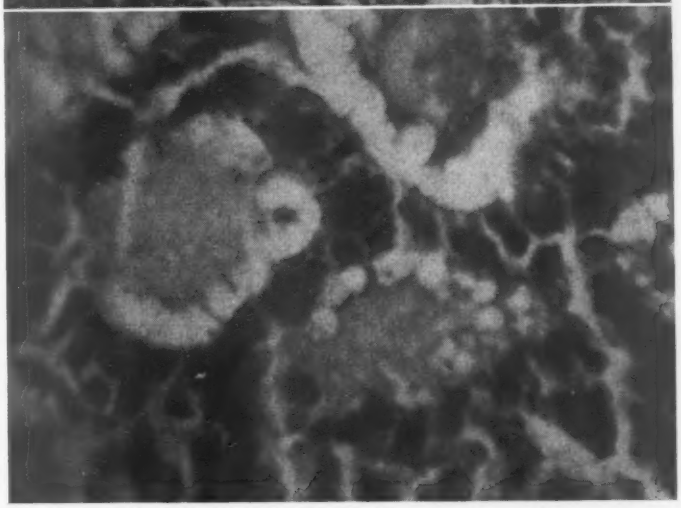

Fig. 3.

Figs. 1-3.—*For legends see opposite page.*

The body of the uterus was slightly enlarged, showing marked congestion. Otherwise the pelvic organs were apparently normal. The right tube and ovary were completely atrophic. Because of the solid portion of the tumor, the liver and the usual lymphatic areas were examined and nothing was demonstrated.

The patient's postoperative convalescence was uneventful. There has been no uterine bleeding in the past 2 years.

Pathologist's Report.—Gross: The specimen consisted of a small amount of endometrium and of a tube and attached cystic ovary. The tube was normal. The ovary measured 18 by 12 cm. The surface was smooth and of a light gray color. Section showed a multilocular cyst with the largest cavity about 10 cm. in diameter. There was a solid portion about 7 cm. in diameter of fibrous character and somewhat polypoid appearance.

Microscopic: The solid portions of the tumor presented a somewhat more vicious appearance than was anticipated from the gross. This was characterized by tubular distributions of columnar epithelial cells, frequently large and dark staining (Figs. 1, 2, and 3). The cellular masses were larger and more solid than are usually encountered (Fig. 4). The stroma was of a nonspecific fibrous character. The lining epithelium of the multilocular portion of the cyst was also of a tall columnar type. In some areas it was distinctly ciliated.

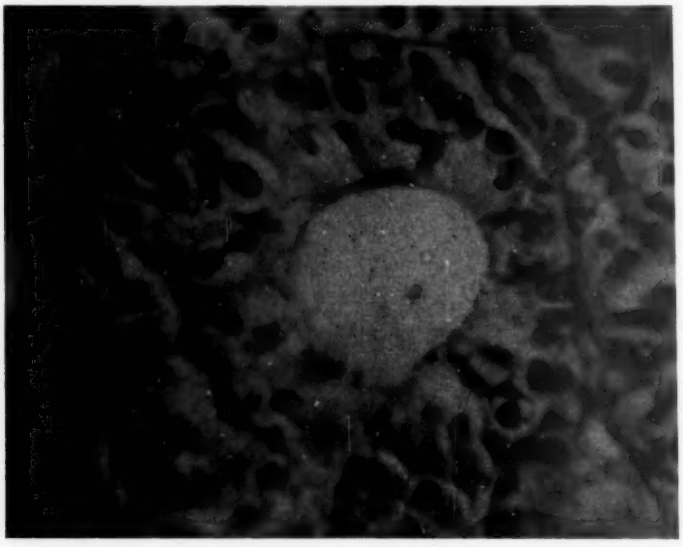

Fig. 4.—High magnification of a single cell nest.

This was considered to be a variant of a Brenner tumor with potentialities of malignancy microscopically. The small endometrial polyps included a few cystic glands supported by fibrous-appearing stroma. They did not show signs of malignancy or evidence of current hyperplasia. The diagnosis was malignant Brenner tumor of the ovary presenting in addition pseudomucinous admixture.

Some slides from the first block cut from the solid portion of the tumor were sent to Dr. Emil Novak for diagnosis. Dr. Novak stated: "It is a most unusual neoplasm, which I personally would interpret as a malignant Brenner tumor of the ovary. At one time we thought all Brenner tumors were benign, and certainly the vast majority are. On the other hand, it has been established beyond any doubt that a very small proportion are malignant, and I believe that this tumor belongs to this group." It was our feeling that some pathologists might look upon portions of these slides as presenting one of the rare adenoacanthomas. This was not the case, however.

For all practical purposes Brenner tumors of the ovary may be considered not to be malignant and not to produce hormones. In addition we may consider these tumors (even the benign class) to be among the rarest neoplasms occurring in the ovary. When unquestioned malignancy is demonstrated in a Brenner tumor the case should be presented and the tumor described. In 1943 I had the opportunity of studying 2 cases of Brenner tumor of the ovary, one of which was of unusual size. This tumor was entirely solid, weighing 5.8 kilograms. We felt that up to this time it was the largest solid Brenner tumor on record. The statement[11] made at that time, "Brenner tumors are of little clinical importance because they rarely reach a size sufficient to cause symptoms, since the cells are undifferentiated sexually they produce no endocrine disturbances, and as far as it is known are never malignant," does not pertain in the light of reported cases of malignancy since 1947.

The histogenesis of quite a few ovarian neoplasms presents very interesting opportunities for theoretical speculation. Brenner[2] in his original description of this tumor in 1907 was of the opinion that histogenetically it arose as a tumor of the follicle and he designated it "oophoroma folliculari." It appears, however, that his line of reasoning did not hold for long and it remained for Robert Meyer to designate it as arising from the islands of indifferent cells first described by Walthard[10] in 1903. Subsequent studies by different authors seem to strengthen this contention. On the other hand, it may be mentioned that Schiller[9] strongly theorized in 1940 a nonovarial source of origin from tissues misplaced into the ovary in fetal life. Spencer and Reel were inclined in 1947 to agree with Schiller but subsequent studies by one of us (P. J. R.) have left the problem again on the doorstep of speculation. Quite frequently Walthard rests are encountered beneath the serosa of the tube but Brenner tumor formation from such rests is exceedingly questionable.

A survey of the literature indicates that a total of 10 cases of malignant Brenner tumor have been previously reported. Dubrauszky[3] in 1949 reported 2 cases of his own and found 2 old cases in the literature. It would be important as well as interesting to study the slides of these tumors. Rawson and Helman[7] brought the total to 6 in 1955. MacKinley[5] added one and Abell[1] reported 3 in 1957. The case herein reported makes the eleventh.

There do not seem to be any suggestive clinical characteristics of these interesting tumors. No cases have been reported in children, unless it be the case of a child aged 6 years, quoted by J. S. Giaccone.[4] More than 50 per cent of all Brenner tumors, benign and malignant, have been reported in patients 50 years of age or older. It is possible that my patient is the oldest in either group (age 84 years). Just how long these tumors may be present in the ovary before removal and identification may be difficult to determine since so many of them are quite small. Their rate of growth even when malignant may be exceedingly slow. This may account for the large percentage being found in women past 50 years of age.

It is generally agreed that endocrine disturbances are not caused by Brenner tumors. When this patient entered the hospital in 1955, the polypoid nature of the endometrium was noted. One year later, in 1956, when she entered the hospital for operation for the ovarian tumor, the endometrium was again showing polypoid change. The question of what might be the causative factor in a recurring polypoid tendency of the endometrium in a patient age 84 years might well be asked. It would be difficult to assume the tumor to be the source of this reaction. A more feasible explanation lies in the probability of postmenopausal extraovarian estrogen production by the adrenal cortex. The postoperative smears made from the vaginal mucosa showed no evidence of stimulation by estrogen.

Since there has been no uterine bleeding in the past 2 years, the question of whether or not the activation of the endometrium was discontinued when the tumor was removed is at once raised. I do not believe this problem can be solved at this time. The only factual statement that can be made, it seems, is that frequently it is still exceedingly difficult to interpret some of the baffling pathologic states that may arise within the structure of the ovary. This no doubt is to be expected since the organ is steeped in embryologic potentialities which are as puzzling today as they were many years ago.

Summary and Conclusion

The case of malignant Brenner tumor of the ovary herein presented is probably the eleventh so far recorded in the literature. The patient with this tumor is the oldest so far noted. The interesting phases pertain to the possibility or probability of estrogen production sufficient to stimulate the uterine endometrium. This reaction if due to estrogen must have had its origin in the suprarenal cortex. It is possible for the Brenner tumor of the ovary to present unquestionable evidence of malignancy though this is exceedingly rare. The chief interest of the tumor lies in the diversification of interpretation of its histogenesis.

I wish to express sincere appreciation of the critical review of this tumor by the late Dr. Emil Novak. In addition the same appreciation is expressed for the pathologic study and diagnosis by Dr. Horace Davidson, Chief of Pathology, Mt. Carmel Hospital.

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A CASE OF ADRENOGENITAL SYNDROME (ADRENAL PSEUDOHERMAPHRODISM) WITH SUBSEQUENT PREGNANCY

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ALTHOUGH chromosomal sex determination occurs during fecundation, we conceive of the direction of the development with its histological changes as becoming manifest for the first time at the seventh or eighth week of embryological life. Much experimental work carried out on laboratory animals and some interesting clinical observations have shown the leading influence of sex hormones on the development of sex organs. As an example of this we can mention the 2 cases of Brentnall[3] and Gaudfroy,[4] who observed pregnancies complicated by ovarian arrhenoblastomas and resulting in the delivery of pseudohermaphroditic infants. Similarly, Zander and Müller[18] described a pseudohermaphroditic newborn infant whose mother was subjected to methylandrostenediol treatment after the removal of a breast sarcoma and they ascribed the abnormality of the external genitals to the use of androgens during pregnancy.

In the light of the foregoing and many other observations, we have enough reason to believe that the heterogeneous sex differentiation in the adrenogenital syndrome represents one form of pseudohermaphroditismus femininus.

In cases of cortical hyperplasia or cortical tumors (adenoma, carcinoma) the secretion of androgenic substances is increased. Under the influence of these substances very interesting changes in habitus, in the external genitals, and in secondary sex characteristics appear, thus giving rise to manifold clinical pictures of hypercorticoidism according to the age and sex of the patient (infant Hercules, macrogenitosomia, female pseudohermaphroditism, Achard-Thiers syndrome).

This article will be confined to the description of a case of cortical adenoma we had the opportunity to follow for many years:

A 14-year-old girl was first admitted on Sept. 18, 1951, to our hospital. According to what her father said, her development had not differed from that of other children until one year previously, at which time an intensive hair growth all over her body commenced. She had not yet menstruated. She began perspiring profusely, and the tone of her voice became lower and coarse. Her figure gradually began to resemble that of a man. The patient had never become seriously ill. She had four brothers and one sister who were well developed and in good health.

Figs. 1, 2, and 3.—Photographs of the patient before treatment.
Fig. 1.—Note masculine physique and evidence of generalized hirsutism despite shaving.

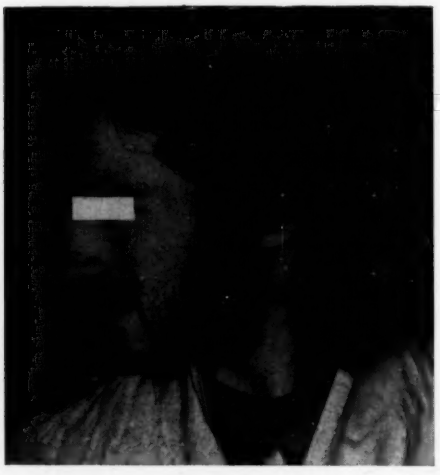

Fig. 2.—Note hirsutism.

Fig. 3.—Hypertrophic clitoris.

Clinical Findings.—Her height was 156 cm., weight 55 kilograms, blood pressure 140/80. The physique was very strong; the behavior and the expression of the face manly; the voice low and rough. The beard, moustache, and the hair of the chest were shaved (Fig. 1). Another picture taken a month after she had not shaved illustrated the strong growth of hair and beard very well (Fig. 2).

Gynecological Examination.—There was a hypertrophic clitoris resembling with its prepuce and the sulcus under it a hypospadiac penis (Fig. 3). Separation of the labia majora disclosed the external urinary meatus and the hymen, which allowed the passage of one finger. The portio vaginalis was small and conical, the vaginal vault shallow and narrow. The uterus was of infantile type, its corpus being as big as a thumb. The adnexa were not palpable.

Fig. 4.—Retroperitoneal air study revealing tumor above right kidney.

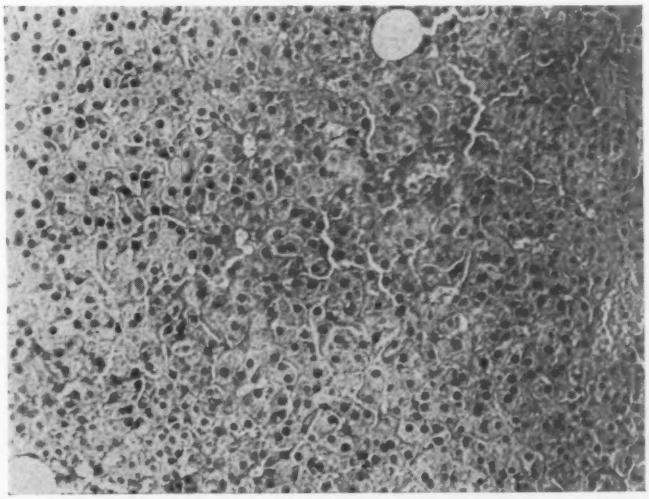

Fig. 5.—Photomicrograph of the adrenal adenoma.

Laboratory Findings.—The hemoglobin was 100 per cent, leukocytes 6,400, and the basal metabolic rate plus 30 per cent. There was no glucosuria or albuminuria. The glucose tolerance test with 50 Gm. glucose after ½ hour was 140 mg. per cent, 1 hour 142 mg. per cent, 1½ hours 140 mg. per cent, and 2 hours 121 mg. per cent. The eye grounds were normal; craniography was normal. The blood sodium was 281.6 mg. per cent, potassium 23.4 mg. per cent, total cholesterol 250 mg. per cent, total lipid 1,500 mg.

per cent. Urinary excretion of 17-ketosteroids was 178.7 mg. per 24 hours. A vaginal smear showed a small number of round basophilic cells or ovaloid cells of basal layers with many leukocytes (atrophic type).

In the presence of the remarkable increase in 17-ketosteroid excretion we decided to perform an x-ray examination of the adrenal glands. Retropneumoperitoneum combined with pyelography disclosed the presence of a round shadow in the right lumbar region above the normal kidney (Fig. 4). The left kidney and corresponding adrenal were normal.

On Dec. 27, 1951, we removed a fist-sized movable tumor, through a vertical incision about 10 cm. lateral to the spinal column, after resection of the twelfth rib. Despite the occurrence of a pneumothorax, the patient recovered without further serious complications. DOCA was prescribed pre- and postoperatively in order to avoid the adrenal cortical insufficiency that might ensue as a result of atrophy of the normal side.

The extirpated tumor was yellowish brown and homogeneous on the cut surface. Microscopically it consisted of light, vacuolated, polyhedral cortical cell trabeculae. Nowhere was there any discernible anaplastic activity.

Fig. 6.—Photograph of the patient 4 months postoperatively, demonstrating breast development.

Histological Diagnosis.—Adenoma of the adrenal cortex (Fig. 5).

Ten days after the operation the 17-ketosteroid excretion amounted to only 17.5 mg. per 24 hours. The blood pressure was 120/80. The sodium was 320 mg. per cent; cholesterol 180 mg. per cent. A glucose tolerance test with 50 Gm. glucose after ½ hour was 103 mg. per cent, 1½ hours 135 mg. per cent, 2 hours 103 mg. per cent.

Four months later the breasts were remarkably developed and hirsutism persisted to only a slight degree (Fig. 6). But despite these important alterations the vaginal smear remained unchanged and it was impossible to get any endometrial tissue by means of a curette.

Contrary to our expectations menstruation did not start even after several more months had elapsed. We then began hormone treatment according to Kaufmann's[20] scheme. Immediately after hormone treatment the patient menstruated for the first time. The bleeding lasted for 3 days and was accompanied by strong pains. This bleeding was followed by another spontaneous menstruation 32 days afterward. A specimen taken at the onset of this period showed histologically an endometrium with premenstrual secretory changes. Repeated assessment of 17-ketosteroid excretion showed 8 mg. in 24 hours.

Meanwhile the patient had gained weight, the hirsutism had almost disappeared, and her body had assumed the graceful character of a young girl's. A subsequent delay

Fig. 7.

Fig. 8.

Figs. 7 and 8.—Photographs of the patient 1½ years after operation, showing evidence of further feminization and absence of hirsutism.

in menstruation responded promptly to Duogynon injections. For further observation we kept the patient in the hospital for a long time. During this period she did not have any other disturbances concerning her periods or her general health. A comparison of the pictures taken before and 1½ years after (Figs. 7 and 8) the institution of the treatment illustrates the almost unbelievable changes which had taken place.

A long time after her discharge the patient again sought medical advice because she was suffering from nausea and vomiting. She had been married Oct. 3, 1955, and her period was 3 months overdue. She had anemia (hemoglobin 46 per cent) and hypotension (90/40), and looked very feeble and exhausted. The 17-ketosteroid excretion was 18.3 mg. per 24 hours. Despite thorough clinical and radiological study we could not elicit any evidence of relapse. Gynecological examination disclosed a normal pregnancy corresponding to the length of amenorrhea. The classical treatment of the vomiting was successful. The patient was discharged in good health but neglected to return to our antenatal clinic.

She was delivered of a healthy girl in her native country, Afyon, by a former assistant of our clinic.

Addendum.—In our department on March 29, 1958, she was delivered of her second child (3,200 grams).

We are indebted to Dr. Yenson for helping us in biochemical examinations, to Dr. Turan for the excellent radiograms, and to Dr. Güçhan for his collaboration in the surgical treatment.

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Obstetrics

HYDATIDIFORM MOLE

A Survey of 66 Cases at Hartford Hospital

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THE purpose of this paper is to present the findings of a survey of 66 cases of hydatidiform mole which occurred at the Hartford Hospital. The clinical features of each case were carefully reviewed and then the microscopic tissue sections from every molar specimen were re-examined. Each mole was then grouped, according to its microscopic appearance, into the classification of hydatidiform moles presented by Hertig and Sheldon[9] and later modified by Hertig and Mansell.[8] In this manner it was possible to correlate the prognosis and outcome of each case with the histopathologic appearance of its molar tissue.

Material

Incidence.—Between Jan. 1, 1938, and Dec. 31, 1956, 65 cases of hydatidiform mole were treated at Hartford Hospital. These occurred in 64 patients; 62 of these were private patients and 2 were ward patients. During this 19 year period there were 93,509 deliveries at this hospital. These figures result in an approximate incidence of one hydatidiform mole per 1,438 deliveries.

The reported incidence of moles varies greatly from one per 145 deliveries[18] to one per 2,500 pregnancies.[13] Our incidence, however, compares more closely with those of Alter and Cosgrove[2] (1:1,720 deliveries) at Margaret Hague Maternity Hospital and Stroup[19] (1:1,488 deliveries) at Pennsylvania Hospital.

One patient had three moles, all treated at this hospital. Her first mole occurred in 1935 prior to the period covered by this study and is, therefore, not included in the figures on incidence. This mole will be included in all further discussion, however, so that the totals will be 66 cases of hydatidiform mole occurring in 64 patients.

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Age.—The reported extremes of this age group are represented by a 12-year-old patient of Bobrow and Friedman[3] and a 55-year-old patient of Feenders.[7] The greatest frequency is reported by Novak[13] to occur in the third decade.

TABLE 1. AGE INCIDENCE

AGE	NO. OF PATIENTS	%
Under 21	7	10.9
21-30	42	65.6
31-40	11	17.2
Over 40	4	6.3
Total	64	

Table I shows the ages of the patients in this series. The greatest incidence (65.6 per cent) occurred in the third decade. The youngest patient was 16 years old; the oldest was 52.

Gravidity.—Hydatidiform moles occur more frequently in multigravid patients, and in this series 22 patients (34.4 per cent) were primigravidas and 42 patients (65.6 per cent) were multigravidas.

Recurrence.—It is uncommon for a patient to have more than one hydatidiform mole. Chesley, Cosgrove, and Preece[5] reviewed the literature in 1946 and found only 41 or 42 cases of recurrent mole. At Hartford Hospital one patient had recurrent moles. The history follows:

M. W. was a 26-year-old gravida i, para 0, white woman. In February, 1935, after 3½ months of amenorrhea, the patient aborted a molar pregnancy and was treated by curettage. In March, 1937, a full-term pregnancy was concluded by cesarean section for cephalopelvic disproportion, and the patient was delivered of a normal infant. In January, 1938, a molar pregnancy was aborted after 2½ months of amenorrhea. The patient was treated by curettage.

In November, 1938, a third mole occurred after 2½ months of amenorrhea. Curettage was done three times, but hormone tests remained positive for 5 months and the uterus remained enlarged for one year. In November, 1939, supravaginal hysterectomy was performed and an enlarged uterus was removed with no evidence of molar tissue or normal pregnancy. The patient is alive and well today.

Symptomatology.—The classical symptoms of hydatidiform mole are a varying period of amenorrhea and enlargement of the uterus followed by irregular uterine bleeding. During the period of amenorrhea the patient may experience the common symptoms of pregnancy (anorexia, morning nausea and vomiting, urinary frequency, breast engorgement, etc.). The vaginal bleeding may take the form of a brownish discharge, spotting, or frank hemorrhage and may or may not be accompanied by lower abdominal cramps. The patient may pass tissue fragments, but the actual passage of grapelike blebs is apparently infrequent. Table II shows the symptoms experienced by the patients in this series. Some patients had more than one symptom.

TABLE II. SYMPTOMS

SYMPTOMS	NO. OF CASES	%
Abnormal vaginal bleeding or spotting	59	89.4
Brownish discharge	4	6.1
Toxemia	3	4.5
Hyperemesis	4	6.1
Pain	9	13.6
Passage of "grapes"	1	1.5
Asymptomatic	1	1.5

The signs and symptoms of toxemia of pregnancy may occur in patients with hydatidiform mole. The incidence of this complication varies in different series.[5, 16] The toxemia usually takes the form of pre-eclampsia. Only 36 cases of eclampsia with mole have been recorded and 5 of these were fatal.[5] Pre-eclampsia rarely occurs in cases of mole before the uterus reaches the level of the umbilicus, but the incidence of toxemia rises rapidly when the uterus enlarges beyond this size.[1, 5, 16] In this series toxemia occurred in only 3 cases (4.5 per cent).

Ovarian cysts frequently accompany hydatidiform moles. These are usually lutein cysts and are frequently bilateral. The reported incidence of ovarian cysts varies between 59 per cent[14] to 16 per cent in a recent series by Stroup.[19] At Hartford Hospital only one patient with mole had detectable ovarian cysts (1.5 per cent).

Month of Gestation.—The period of amenorrhea prior to the onset of symptoms in patients with hydatidiform mole varies greatly. In this series 54.5 per cent of the patients were in the first trimester of pregnancy when abnormal symptoms occurred which eventually led to the diagnosis of mole. These data are shown in Table III.

TABLE III. GESTATIONAL AGE OF HYDATIDIFORM MOLES

MONTH OF GESTATION	NO. OF CASES	%
1-3 months	36	54.5
4-6 months	24	36.4
7 months	6	9.1

Size of Uterus.—One of the characteristics of hydatidiform mole is a disparity between the period of amenorrhea and the size of the pregnant uterus. The uterus may be of a size which is compatible with the duration of the pregnancy, but more often it is either larger or smaller than expected. Lull and Kimbrough[10] stated that the uterus is larger than expected in 50 per cent of cases. In 57 cases Chesley and his associates[5] found the uterus larger than expected in 33 per cent, and Stroup[19] reported similar findings in 66 per cent. Table IV indicates that in our experience the frequency of a smaller uterus was only slightly less than that of a larger uterus.

TABLE IV. SIZE OF UTERUS

SIZE	NO. OF CASES	%
Smaller than period of gestation	19	28.8
Same size as period of gestation	19	28.8
Larger than period of gestation	24	36.4
No information	4	6.1

Diagnosis

The clinical diagnosis of hydatidiform mole is based upon the history, symptomatology, and the physical findings as outlined above. The proved diagnosis is made when tissue is obtained and examined microscopically by the pathologist.

The possibility of hydatidiform mole should be suspected in any case in which (1) the uterus is enlarging rapidly beyond the expected size; (2) the uterus fails to grow as expected for the duration of the pregnancy; (3) symptoms of toxemia develop during the first trimester; or (4) irregular spotting or staining occurs during pregnancy. Mueller and Lapp[12] believed that a fullness in the lower uterine segment with bulging into the cul-de-sac is an important sign peculiar to cases of mole.

The diagnosis of hydatidiform mole may be facilitated by the use of quantitative chorionic gonadotrophin hormone tests. It must be remembered, however, that the chorionic gonadotrophin titer in a normal pregnancy rises sharply until approximately the twelfth week, after which there is a steady decline until the termination of the pregnancy. In cases of mole and choriocarcinoma, the titer does not fall after the twelfth week but continues to increase until all remnants of chorionic tissue are removed from the patient. Consequently, hormone tests are useful in the diagnosis of hydatidiform mole only after the first trimester when there is an appreciable, measurable difference in the chorionic gonadotrophin titer in the normal and the abnormal pregnancy.

Quantitative determinations of the chorionic gonadotrophin titer are usually performed on 24 hour urine samples. It has been our practice to use this method with immature female white rats as the test animal. Similar hormone tests can be performed on cerebrospinal fluid and on the blood serum. McCormick[11] reported that the spinal fluid chorionic gonadotrophin titer reaches a level high enough to cause a positive test only in cases of hydatidiform mole and choriocarcinoma.

Delfs[6] has reported excellent results with the use of blood serum to determine chorionic gonadotrophin titers. After the first trimester the hormone level is high enough in the serum to give a positive diagnosis in suspected cases of mole.

One other diagnostic test has been reported by Borell, Fernstrom, and Westman.[4] In a small series of cases they have performed pelvic arteriograms and have reported characteristic findings in cases of mole and choriocarcinoma.

Because of the signs and symptoms of this disease the preoperative diagnosis is usually incomplete, threatened, or missed abortion. Table V shows the preoperative diagnoses in this series; in 27.3 per cent the diagnosis was hydatidiform mole and in 62.1 per cent the diagnosis was abortion of one type or another.

TABLE V. PREOPERATIVE DIAGNOSES

PREOPERATIVE DIAGNOSIS	NO. OF CASES	%
Incomplete abortion	22	33.3
Complete abortion	1	1.5
Inevitable abortion	3	4.5
Threatened abortion	5	7.6
Missed abortion	10	15.2
Hydatidiform mole	18	27.3
Pregnancy	2	3.0
Ruptured ectopic pregnancy	1	1.5
Dysfunctional uterine bleeding	1	1.5
Fibroid uterus	1	1.5
Diagnosis deferred	2	3.0
	66	

Treatment

The only cure for hydatidiform mole is evacuation of the uterus, and this should be performed as soon as the diagnosis is established. It is generally agreed that a dilatation and curettage can be done safely on all uteri which are smaller than a 12 weeks' pregnancy. In larger uteri abdominal hysterotomy is the procedure of choice. Novak[15] preferred to evacuate the uterus vaginally with a sponge forceps and 4 or 5 days later do a careful curettage when the uterus is partially involuted. In patients over 35 or those with a completed family, he preferred to do a hysterectomy with the mole in situ.

All patients who have a hydatidiform mole must have a careful follow-up for at least one year. The only method of following these patients is by repeated chorionic gonadotrophin tests, since this is the only test which will give any information as to the course and prognosis of the condition. Most authorities believe that these tests should be performed once or twice a month for 3 months and then monthly until a year has passed since delivery of the mole. If at any time within a year the titer rises (in the absence of pregnancy) a repeat curettage and possibly hysterectomy are indicated.

If the chorionic gonadotrophin tests remain positive following the evacuation of a hydatidiform mole, there are four possibilities: (1) there is residual trophoblastic tissue in the uterus; (2) chorioadenoma destruens or choriocarcinoma is present; (3) enlarged, cystic ovaries are present; and (4) the patient is pregnant. Because of the differential diagnosis presented by a positive test and because of the subsequent treatment, all patients should be instructed to avoid becoming pregnant for at least one year following a hydatidiform mole.

Table VI shows the treatment given to patients with hydatidiform mole at Hartford Hospital. Forty-nine cases (74.2 per cent) required nothing more than one curettage. Five other cases required more than one curettage. An additional five cases required repeated curettage followed by hysterectomy.

TABLE VI. TREATMENT

TREATMENT	NO. OF CASES	%
Curettage	49	74.2
Hysterotomy	3	4.5
Hysterectomy (primary treatment)	2	3.0
Salpingectomy	1	1.5
No treatment	1	1.5
Curettage twice	5	7.6
Curettage twice, followed by hysterectomy	5	7.6
	66	

In the majority of cases, the chorionic gonadotrophin tests become negative within 2 months after evacuation of the mole. Table VII shows our results: tests were negative in 47.0 per cent of cases within 2 months and in an additional 13.6 per cent within 6 months. In 3 cases the tests remained positive.

TABLE VII. INTERVAL BETWEEN EVACUATION OF MOLE AND FIRST NEGATIVE CHORIONIC GONADOTROPHIN TEST

TIME BETWEEN EVACUATION OF MOLE AND FIRST NEGATIVE TEST	NO. OF CASES	%
Less than 1 month	5	7.6
1-2 months	26	39.4
2-3 months	7	10.6
3-6 months	2	3.0
No tests taken	18	27.3
Unknown	5	7.6
Tests remained positive	3	4.5
	66	

Course and Prognosis

Hydatidiform mole can definitely (although infrequently) give rise to choriocarcinoma, and for this reason a mole is considered a premalignant condition. According to Park and Lees,[17] 90 to 99 per cent of moles are not followed by choriocarcinoma and 50 to 60 per cent of choriocarcinomas are not

preceded by moles. In the experience at Hartford Hospital, hydatidiform mole has been a relatively benign disease. Table VIII summarizes the results. Of the total of 64 patients, 60 are living and well, 2 patients are known to be

Fig. 1.

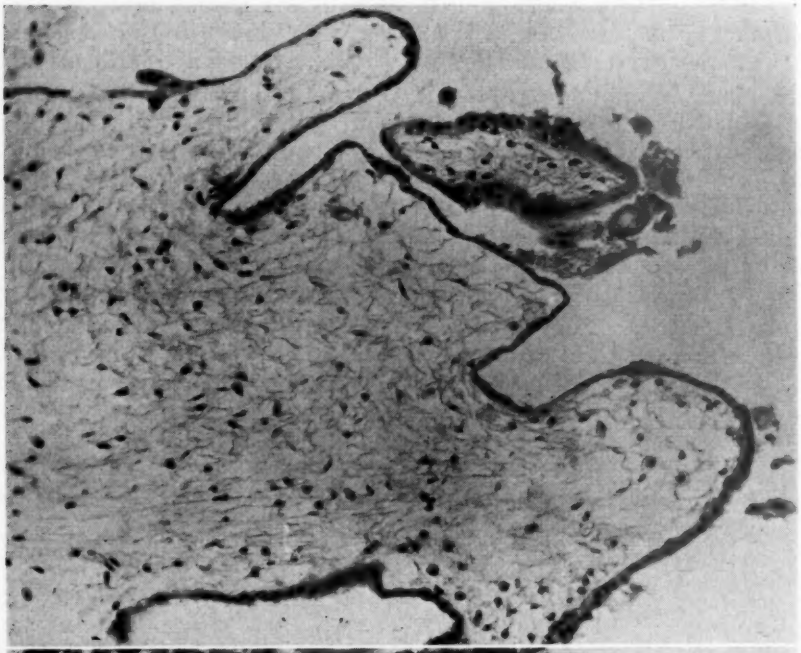

Fig. 2.

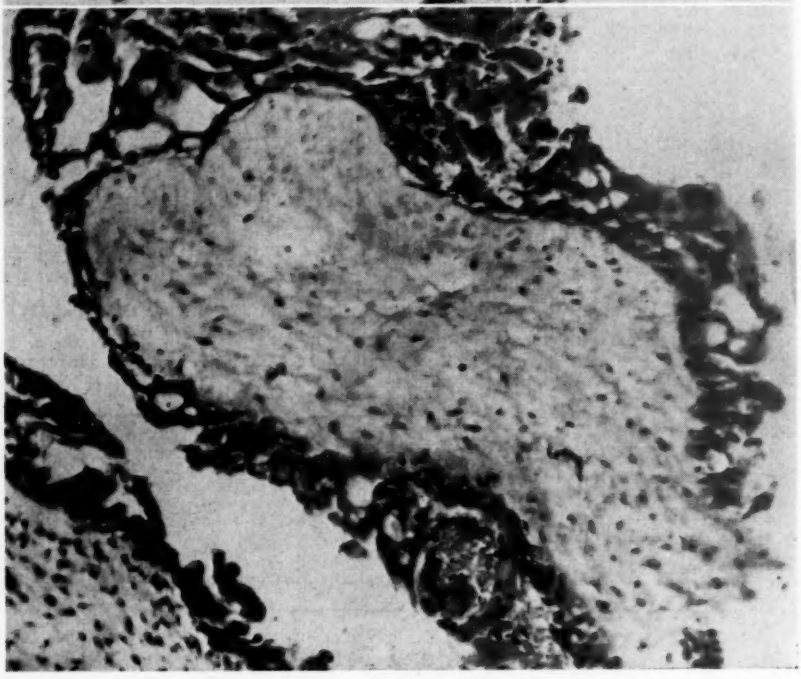

Fig. 1.—Hydatidiform mole. Grade I. There is a minimal amount of trophoblastic hyperplasia. (Hematoxylin and eosin. ×100; reduced ¼.)

Fig. 2.—Hydatidiform mole, Grade II. There is moderate proliferation of trophoblastic cells. (Hematoxylin and eosin. ×100; reduced ¼.)

TABLE VIII. COURSE OF DISEASE

COURSE	NO. OF PATIENTS	%
Uneventful with complete recovery	60	93.8
Lost to follow-up	2	3.1
Known dead	2	3.1
	64	

Fig. 3.

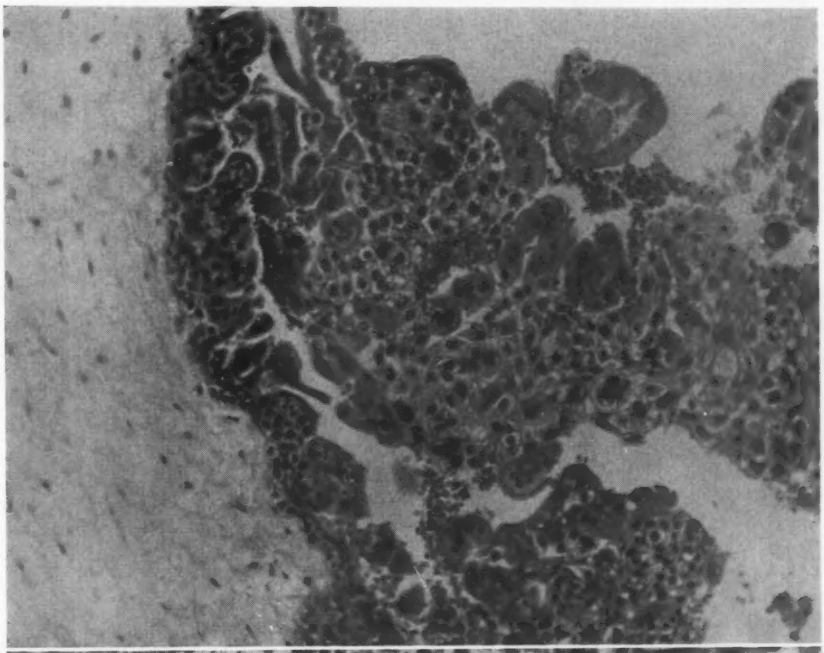

Fig. 4.

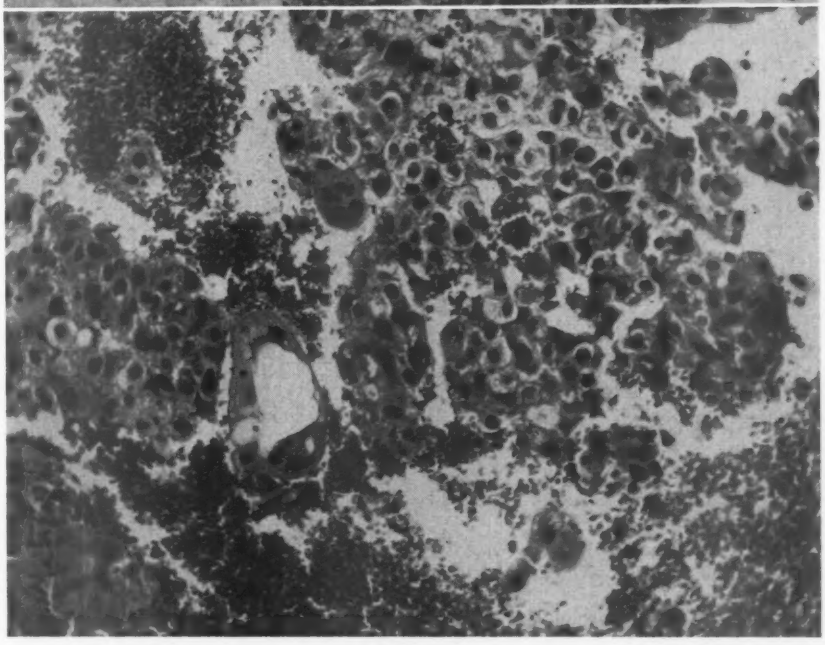

Fig. 3.—Hydatidiform mole. Grade III. There is marked hyperplasia of the trophoblast. (Hematoxylin and eosin. ×100; reduced ¼.)

Fig. 4.—Hydatidiform mole, Grade III. There is anaplastic proliferation of the trophoblast with no evidence of formation of villi. (Hematoxylin and eosin. ×100; reduced ¼.)

dead, and 2 have been lost to follow-up. Seven patients underwent hysterectomy. Eleven of the patients had their moles during 1956; and, of the remaining 46 patients, 33 (71.7 per cent) are known to have had subsequent pregnancies since the moles.

Fig. 5.

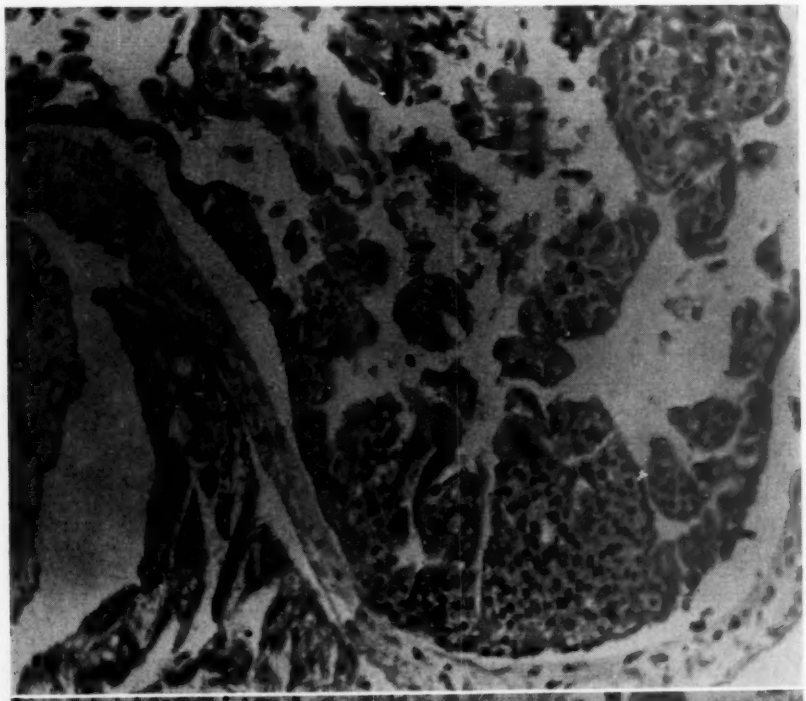

Fig. 6.

Figs. 5 and 6.—Chorioadenoma destruens. Uterine wall showing invasion of the myometrium by trophoblastic tissue. There is markedly atypical trophoblastic proliferation but there is definite formation of villi. (Hematoxylin and eosin. ×100; reduced ¼.)

The microscopic tissue slides of all cases of hydatidiform mole were meticulously re-examined. Then, depending upon its histologic appearance, each mole was graded according to the classification established by Hertig and

Fig. 7.

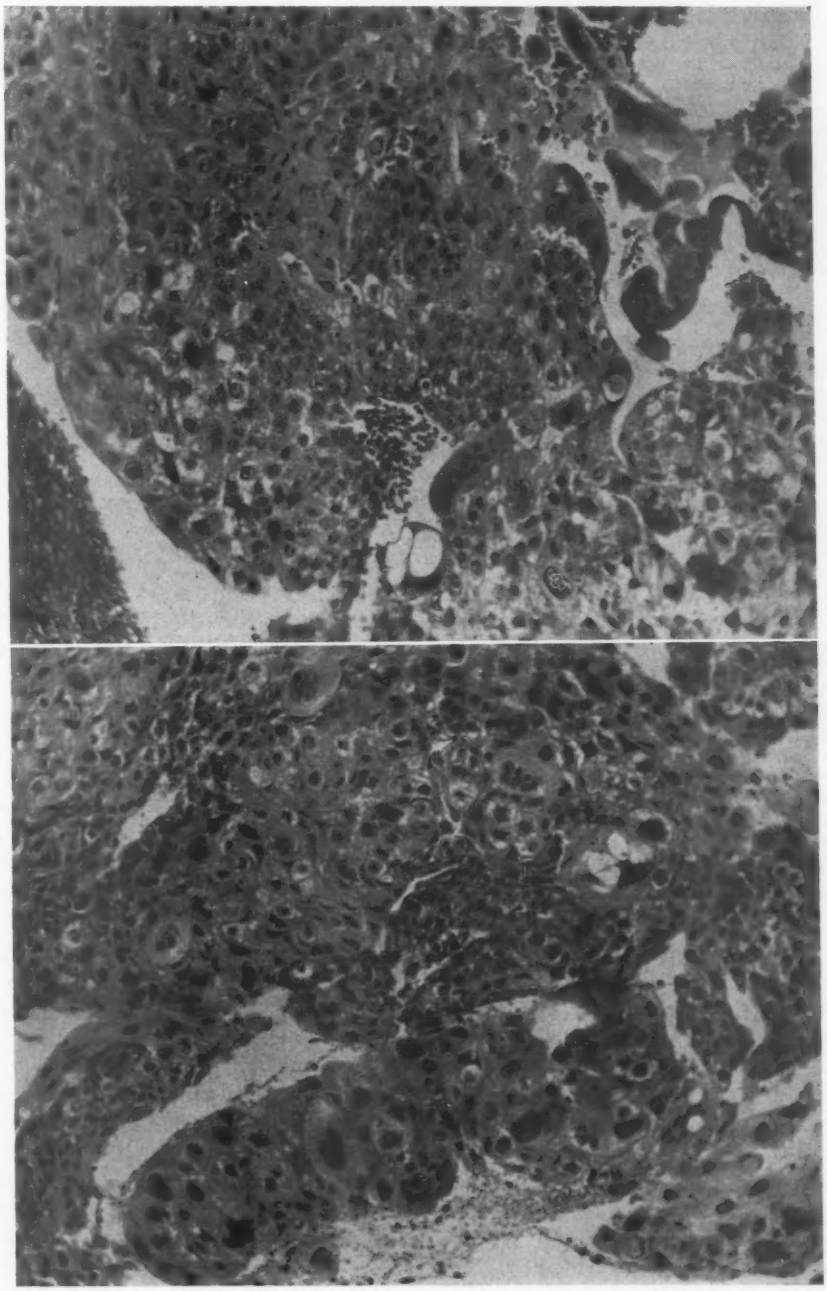

Fig. 8.

Fig. 7.—Hydatidiform mole, Grade III. There is marked trophoblastic hyperplasia and the cells show moderate hyperplasia. (Hematoxylin and eosin. ×100; reduced ¼.)

Fig. 8.—Choriocarcinoma. The specimen consists of uterine curettings which contain anaplastic trophoblastic cells without evidence of villi. (Hematoxylin and eosin. ×100; reduced ¼.)

Mansell.[8] According to these investigators, there are three grades of moles: Grade I, the apparently benign moles in which there is only slight hyperplasia of the trophoblast; Grade II, the potentially malignant moles in which there is moderate hyperplasia with moderate anaplasia of the trophoblast; and Grade III, the apparently malignant moles in which marked anaplasia accompanies the hyperplasia of the trophoblast.

TABLE IX. CLASSIFICATION OF HYDATIDIFORM MOLES AND FOLLOW-UP

GRADE	FOLLOW-UP
Grade I (apparently benign)	34 Living and well 1 Dead, *C. welchii* septicemia
Grade II (potentially malignant)	27 Living and well 1 Dead, cardiac disease. Chorioadenoma destruens
Grade III (apparently malignant)	3 Living and well 1 Chorioadenoma destruens 1 Choriocarcinoma 1 Tubal pregnancy

In this series there were 35 cases of Grade I moles. Of these, 34 patients are living and well. One patient in this group died on the first postoperative day of a fulminating *Clostridium welchii* septicemia.

Fig. 1 is a photomicrograph of a typical Grade I mole in which there is a minimum of trophoblastic proliferation.

In the Grade II classification there were 28 cases. Twenty-seven of these had uneventful recovery. One patient had a hysterectomy after the mole, and the specimen showed chorioadenoma destruens. She died 2½ years later in another hospital; no autopsy was performed. The final diagnoses were myocardial infarction, hypertension, and arteriosclerosis.

Fig. 2 demonstrates a Grade II mole. In this case there is moderate hyperplasia of the trophoblastic cells.

In the Grade III classification there were 3 cases, all of which are of particular interest.

Figs. 3 and 4 are photomicrographs of typical Grade III moles. Fig. 3 illustrates marked hyperplasia of the trophoblast, and Fig. 4 demonstrates the trophoblastic anaplasia which can occur in this category of moles.

The first patient with a Grade III mole had a repeat curettage after the mole was examined microscopically. The second specimen was diagnosed as choriocarcinoma. She had a radical hysterectomy with bilateral salpingo-oophorectomy. Since operation she has had 26 negative chorionic gonadotrophin tests and is alive and well 8 years postoperatively. Review of the slides of this case indicated that the original diagnosis should have been chorioadenoma destruens. Figs. 5 and 6 demonstrate representative sections of the uterine wall in which the myometrium is invaded by trophoblastic tissue. Although the trophoblast is markedly atypical, it forms a definite villous pattern.

The second patient with a Grade III mole also had a repeat curettage. These curettings were examined by several independent pathologists and were diagnosed as choriocarcinoma. The patient underwent total hysterectomy and bilateral salpingo-oophorectomy. Postoperatively the chorionic gonadotrophin test became negative and the patient had an uneventful course. She is now alive and well 7 years after operation and apparently represents one of the rare recoveries from choriocarcinoma.

Fig. 7 shows the Grade III mole with marked proliferation and anaplasia of the trophoblast. Fig. 8 illustrates the microscopic appearance of the uterine

curettings which show anaplastic trophobalstic cells without evidence of villus formation. The diagnosis of choriocarcinoma was based upon these curettings.

The third patient with a Grade III mole had a ruptured tubal pregnancy and underwent salpingectomy. The operative specimen showed a hydatidiform mole with marked trophoblastic proliferation and mitoses and anaplasia of the Langhans and the syncytial layers. This patient is well 6½ years after operation. She has had no further pregnancies.

Table IX shows the classification of the moles and their course.

Summary

A survey of 66 cases of hydatidiform mole treated at Hartford Hospital from 1938 to 1956 has been presented.

The clinical characteristics of these cases have been described and compared with those cited in similar studies reported in the literature.

A brief discussion of the diagnostic and therapeutic principles of this condition has been presented.

Each case of hydatidiform mole has been re-examined microscopically and grouped by Hertig's classification.

The final statistics suggest that hydatidiform mole is a benign condition which is rarely followed by malignant complications. Of the 66 cases in this series, there was successful recovery in 64. Of these, one patient had what appears to be a true choriocarcinoma and has survived 7 years. Another patient had a chorioadenoma destruens and has survived 8 years. Of the 2 deaths, one patient died of septicemia on the first postoperative day. The other patient died of cardiac disease 2½ years after the diagnosis of chorioadenoma destruens had been made.

I wish to express my sincere appreciation to Dr. Robert Tennant, of the Pathology Department of Hartford Hospital, who examined the microscopic slides, classified each mole, and prepared the photomicrographs. Without his knowledge, cooperation, and assistance, this study and this paper would not have been possible.

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CAN PRIMARY PULMONARY CHORIONEPITHELIOMA DEVELOP AFTER A TERM PREGNANCY?

Case Report

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IN PRIMARY pulmonary chorionepithelioma, the lung parenchyma is the site of development of chorionepithelioma after the benign chorionic cell has been transported there from the placenta.

Nearly all cases of pulmonary chorionepithelioma are metastatic in nature from a primary focus which develops at the point of implantation of the fertilized ovum. In a study of 32 cases of uterine chorionepithelioma with metastasis,[1] the lungs were found to be affected in 93.75 per cent. The lungs were the first target of metastasis in 14 and the second target of metastasis in 16, making a total of 30 cases of pulmonary metastases in 32 cases of uterine chorionepithelioma.

Acosta-Sison[2] has reported 3 cases of generalized chorionepithelioma in which the uterus was apparently not involved. That this phenomenon is not peculiar to the Philippines was shown by Willis,[3] who cited many German and other European authors. The case here presented seems to belong to this group.

A. G., 24 years old, gravida iii and para iii, was admitted in the medical ward of the Philippine General Hospital on March 3, 1957, for the complaint of vomiting, epigastric pain not related to meals, productive cough, weakness, and headache. She had had 3 pregnancies ending in term liveborn babies. Her last delivery was on Jan. 3, 1957, or 2 months previously.

On admission, she was found to be fairly well developed, slightly undernourished and pale, with a temperature of 37.1° C., a pulse rate of 92 and a respiratory rate of 26. The blood pressure was 140/90 mm.

Abdominal and pelvic examinations were negative. X-ray of the chest showed a rounded density 6 by 8 cm. at the upper portion of the lower lobe of the left lung, with a central cavity. The radiologist interpreted the shadow as a malignant growth which he regarded as not metastatic.

On the second hospital day, erythrocyte count was found to be 3.72 million; the leukocyte count 12,400. On the eleventh hospital day the red blood cells had dropped to 1.02 million, while the white cell count rose to 21,350. There was no external bleeding and the stools, though dark, were reported as negative for occult blood. A frog test of the urine was positive.

On the ninth hospital day, the patient complained of dimness of vision and of photophobia. On the eleventh day she became unconscious. Lumbar puncture at this time showed clear, colorless spinal fluid. She died 8 hours after losing consciousness, or 2 months and 11 days after her last term delivery.

At autopsy the peculiar findings as noted by the pathologist, Dr. B. D. Canlas, were as follows:

1. The left lung showed at the upper portion of its lower lobe a large encapsulated growth, 8 by 6 by 5 cm., with a necrotic center which under the microscope revealed marked necrosis, hemorrhage, inflammatory cells, and Langhans and syncytial cells at the periphery.

2. The well-involuted uterus, which grossly appeared normal, was subjected to 52 sections, producing 112 slides which were examined microscopically in the search for a focus of malignancy. One slide of the thirty-fourth section showed a chorionic embolus in a blood vessel in the depths of the myometrium (Fig. 1). The embolus had not yet broken through the vascular wall. The rest of the uterus was normal. The tubes, ovaries, vagina, bladder, and parametrium also appeared normal and free from chorionic growth. Both ovaries contained only lutein cysts.

3. Mutiple metastases were present in the lungs, liver, kidneys, spleen, occipital lobes of the brain, and beneath the mucosa of the whole extent of the jejunum and ileum. The myocardium showed two emboli similar to the one seen in the myometrium. They were still within the confines of the vascular wall.

4. The right kidney showed beneath its capsule a massive perirenal hematoma consisting of 800 c.c. of blood. Besides the presence of metastatic growths, there were infarcts in the spleen, liver, and kidneys. There was phlebothrombosis of the ovarian plexus of veins.

5. The thyroid gland showed coexisting papillary adenocarcinoma in the left lobe.

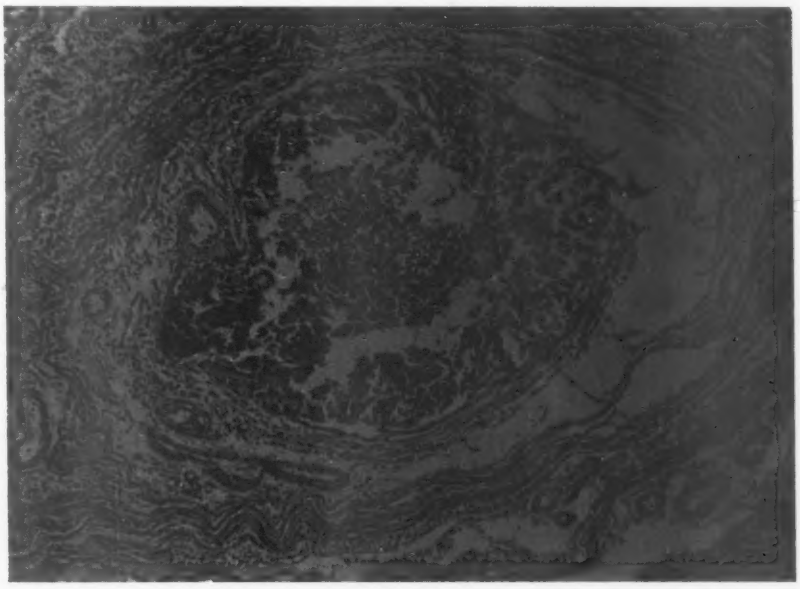

Fig. 1.—Chorionic embolus in a myometrial vessel.

Comment

This 24-year-old patient, 2 months and 11 days after a normal term delivery, died of generalized choriocarcinoma which apparently had disseminated from choriocarcinoma in the left lung. The genitals were free from the growth except for an embolus seen in a vessel in the myometrium. The cells of this embolus had not yet broken through the vascular wall.

The question may be asked as to whether the primary lesion may have originally been in the uterus and eventually regressed or been cast off. The patient did not have postpartum hemorrhage or a curettage to explain the disappearance of the growth. Perhaps the embolus seen in the vessels in the thirty-fourth section made in the uterus represents the primary chorionic growth. On the other hand, the embolus may have been metastatic from another primary source.

In cannot be denied that the chorionic cell must have originally resided in the uterus. It is a well-known fact that, during pregnancy, chorionic cells often are deported by the circulation to the lungs and other regions. Since the cells are very rarely malignant, however, they disappear or are absorbed without causing any harm to the patient.

It has been pointed out[2] that, in chorionepithelioma resulting from pregnancy, not all the chorionic cells are malignant, and indeed the majority are benign. If these malignant cells happen to attach themselves to the uterus, they will give rise to a primary malignant growth there. If, however, the specific malignant cells are carried by the circulation elsewhere, they will give rise to malignancy wherever they may be transported and lodge.

The size of the chorionepithelioma in the lower lobe of the left lung makes it appear to be the oldest of all the growths found in the different organs and points to the left lung as the primary site of chorionic malignancy. From this primary site in the left lung, there apparently occurred dissemination through the circulation as indicated by the presence of multiple arterial chorionic emboli.

Conclusion

The evidence presented by this case is that chorionepithelioma may arise primarily in an extragenital site, in this case the lung, from benign or only potentially malignant cells transported through the circulation from an apparently normal placenta.

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MATERNAL MORTALITY IN THE EPIDEMIC OF ASIAN INFLUENZA, NEW YORK CITY, 1957

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THE epidemic of Asian influenza which began in China early in 1957 came to the attention of American investigators in April, when it reached Hong Kong. Laboratory investigation in this country indicated that the epidemic was caused by a variant of influenza A virus, not hitherto described, which was immunologically different from the types of that virus previously encountered.[1] The epidemic spread rapidly in the Far East and soon reached other continents than Asia. There seemed little reason to doubt that the virus would be seeded in this country and cause an epidemic, since the population had had no experience with the causative agent and had not built up any immunity against it.

Efforts were made to develop a vaccine against the Far Eastern strain of influenza A virus. It was realized, as a result of experiments with previous influenza A vaccines containing other strains of the virus, that a vaccine containing 400 to 700 chicken cell agglutinating units in 1 ml. was desirable.[3] On account of the rapidity with which the epidemic was spreading, however, a monovalent vaccine containing 200 CCA units of influenza A virus (FE strain) in 1 ml. was considered to be the one which could be produced most rapidly and the use of which might give a fair degree of immunity to Asian influenza.[2] Actually, not enough vaccine reached the public until the end of October. By that time the epidemic in New York City had passed its peak. Although the Department of Health offered the vaccine free to antenatal clinics from the meager supply it had purchased, few pregnant women were injected with it before the epidemic period. None of the patients discussed here received influenza vaccine.

The first cases of influenza to occur in New York City were in persons newly arrived from Europe and the Far East during August. As more and more such persons came into the country and as individuals from epidemic areas in the United States came to the city, there was a gradual building up of cases during September. It was during the last week end of that month that the epidemic hit with full force and it reached its peak during the following week. Thereafter it receded gradually, and the situation returned to normal by the end of November. Deaths from influenza and pneumonia began to be reported in October and continued to be reported throughout that

and the next month. It soon became obvious that most deaths occurred in old people, particularly those with atherosclerotic heart disease. A considerable percentage of the deaths occurred in young adults, however, particularly in those suffering from rheumatic cardiac conditions and in pregnant women. The combination of the two was a special risk.[4]

Table I lists the number of deaths from all causes in women who were pregnant or who were not more than 6 months post partum during the years 1953 to 1957. It will be noted that although the number of deaths varied from month to month and year to year, the only month when a significantly large number of deaths was recorded was in October, 1957. In Fig. 1 the total mortality for the city from August, 1957, to March, 1958, as well as the maternal mortality for the same period, is charted by week. It will be noted that there was an excess of total mortality during October, 1957, and that there was also an excess of maternal deaths in that period. The curve for the previous year does not show a similar rise, nor was there a rise in the years 1953-1956 (Table I).

TABLE I. DEATHS FROM ALL CAUSES IN PREGNANT WOMEN, NEW YORK CITY, 1953-1957

MONTH	1953	1954	1955	1956	1957
January	16	22	9	9	12
February	16	5	9	12	14
March	15	15	11	12	12
April	8	15	13	18	17
May	10	7	9	10	11
June	20	10	15	12	14
July	15	13	7	11	12
August	7	12	14	11	12
September	13	18	19	10	19
October	10	12	9	9	31
November	10	8	11	12	15
December	11	13	10	18	9
Total	151	150	136	144	178

An epidemiological history was obtained in all maternal deaths in which the diagnosis of influenza was made, during the epidemic period. There were 22 in a total of 216 deaths from influenza in the city. There were, in addition, 4 deaths of women who became ill more than one month post partum. These are not included in the present study. Sixteen of the women were white, 4 were nonwhite, and 2 were listed as Puerto Rican. There were 13 on ward and 9 on private services. The gravidity was as follows:

GRAVIDITY	NUMBER
i	4
ii	7
iii	3
iv	3
v	1
vi	2
vii	1
?	1

Table II indicates the ages of the mothers who died. These correspond to the ages for pregnancy in the general population. About 73 per cent of the pregnancies were in women between 20 and 29 years of age.

The gestational age and the condition of the fetus at the time of the mother's death are shown in Table III. Six infants were born alive and continued to live. The gestational ages were 40 weeks in 4 and 36 weeks and

37 weeks, respectively, in the other 2. All the mothers died after being delivered, one on the same day; one on the following day; one, 2 days later; and one each, 5, 6, and 9 days after birth. Four infants were born dead, one at 21 weeks, one at 33, and 2 at 39 weeks of gestation. The one at 33 weeks was delivered by cesarean section immediately after the mother's death. Two of the women died one day after being delivered of the stillborn infant and one died 2 days later. In 12 instances the pregnant woman died with the fetus in utero.

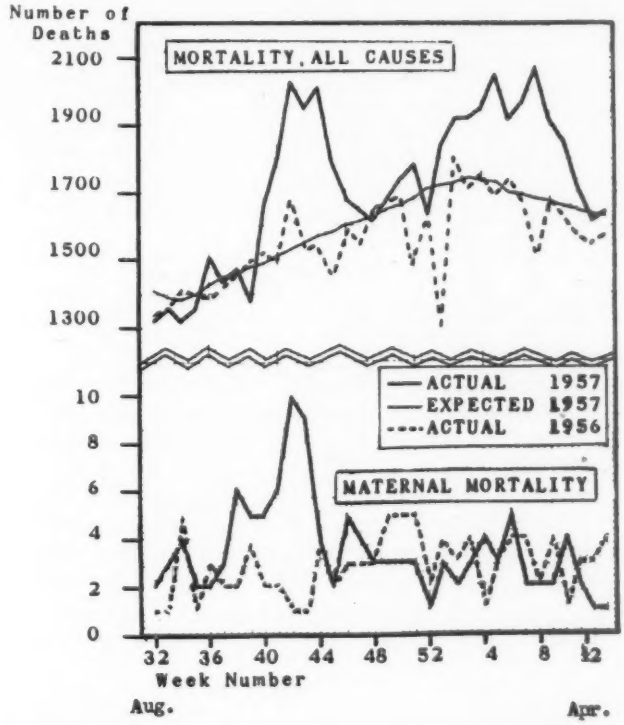

Fig. 1.—Weekly mortality from all causes, actual and expected, and maternal deaths, New York City, August, 1957, to March, 1958.

TABLE II. AGES OF PREGNANT WOMEN WHO DIED OF INFLUENZA IN NEW YORK CITY, OCTOBER AND NOVEMBER, 1957

AGE	NO.
15-19	2
20-24	8
25-29	7
30-34	1
35-39	3
40+	1
Total	22

The elapsed period between the onset of influenza and death was less than one day in one case, 1 to 3 days in 4, 4 to 6 days in 8, and 1 to 2 weeks in 7.

Complications at the time of delivery occurred in 2 instances where there was a live birth. In one there was a premature separation of the placenta (37 weeks' gestational age) and in the other, born at 40 weeks, the

placenta had to be extracted manually. Of the infants born dead, one was delivered spontaneously at 21 weeks of fetal age, one was delivered by cesarean section at 33 weeks of fetal age, after the mother's death. In the other 2 cases there was abruptio placentae in one and pre-eclampsia in the mother in the other. The most striking complication of pregnancy was rheumatic cardiac disease, which was present in 7 of the women.

TABLE III. GESTATIONAL AGE OF PREGNANT WOMEN WHO DIED OF INFLUENZA, AND CONDITION OF THE FETUSES AT THE TIME OF THESE DEATHS IN NEW YORK CITY, OCTOBER AND NOVEMBER, 1957

GESTATIONAL AGE (WEEKS)	NO.	CONDITION OF FETUS		
		BORN ALIVE	STILLBORN	NO DELIVERY
8	1			1
10	1			1
16	2			2
20-24	4		1	3
25-28	2			2
29-32	2			2
33-36	4	2	1	1
37-40	6	4	2	0
Total	22	6	4	12

Laboratory confirmation of influenza was obtained in 6 instances. In one, the Asian strain of influenza virus A was recovered from the throat and in 3 it was isolated from the lungs at autopsy. A rise in antibody titer of the serum was found in 2 instances. Influenza virus was also isolated from the lungs of one of the stillborn infants. Blood counts were done on 18 of the sick women. In 15 the white-blood-cell count was above 10,000 per cubic millimeter, with a high polymorphonuclear percentage. In 3 instances the white-blood-cell counts were between 3,500 and 5,000 and the polymorphonuclear percentage was from 54 to 56. The course of illness in most of the cases that ended fatally was rapid and progressive in spite of excellent medical care:

J. S., a 23-year-old woman who was 21 weeks pregnant, was seen in the antenatal clinic on October 7. This was her fifth pregnancy. She had had three cesarean sections in 1953, 1954, and 1956, and a therapeutic abortion in 1952. At the age of 13 years she had had pulmonary tuberculosis for which she was treated for 27 months when it became arrested. She was examined in the clinic; she had no fever. There were musical, wheezing râles on both sides of the chest, but no moist râles. She was known to have asthma and she stated that she had been wheezing for 2 days. She was given medication and sent home. On the morning of October 9 she came to the emergency room complaining that her wheezing was not improved. Her temperature was 98.4° F., pulse 140, and respirations 32 per minute. She was given aminophylline suppositories and other medication and sent home. She returned in the afternoon; at this time she had a fever of 104.8° F., pulse 160, and respirations 42 to the minute. She complained of cough, chest pains, and dyspnea, and had copious amounts of rusty-looking sputum. She was admitted to the ward, where a diagnosis of pneumonia, right side, was made. This was confirmed by an x-ray film. She was placed in an oxygen tent and started on large doses of penicillin intravenously.

On admission a blood culture had been done, which was sterile. Throat culture yielded *Staphylococcus aureus,* coagulase positive. It was resistant to penicillin and Achromycin, but sensitive to bacitracin, Chloromycetin, and streptomycin. The red-blood-cell count was 3.5 million with hemoglobin 10 Gm. The white-blood-cell count was 4,700 with

78 per cent polymorphonuclear cells, 16 per cent lymphocytes, and 6 per cent monocytes. The hematocrit was 41 per cent. The urine had a specific gravity of 1.070, was alkaline, and showed a trace of albumin, 2 plus sugar and 3 plus acetone.

Parenteral fluids were started to combat the dehydration and acidosis, and as soon as the report of the sensitivity tests was received the patient was put on Chloromycetin, 3 Gm. a day, intravenously, and streptomycin, 2 Gm. a day, intramuscularly. In spite of these measures the patient did not improve. The next morning her temperature was 100.2° F. and she appeared less cyanotic. Her dyspnea, however, was still marked and she appeared weaker. Frequent suction of the throat was needed to remove thick, tenacious, blood-tinged sputum. She passed a 4 month old fetus, weighing 330 grams, at 10:35 A.M. The placenta was intact and the fundus hard. She grew more dyspneic, however, and a tracheotomy was performed at noon. In spite of all therapeutic measures she died that night at 7. P.M.

Postmortem examination was made at 11 A.M. the next morning, October 11. There was an acute, severe tracheobronchitis and lobular pneumonia, bilateral, severe and confluent. There was an old, healed tuberculosis. Culture of the lung yielded influenza virus A, Far Eastern strain, as well as *Staphylococcus aureus*, coagulase positive.

Comments

In the epidemic of influenza A (Asian strain), which occurred in New York City in October and November, 1957, it is estimated that about 8 to 10 per cent of the population became ill. Most of those affected were under 20 years of age. Mortality, however, was chiefly in old people suffering from chronic disease, especially atherosclerotic heart disease. Of the 216 deaths, 123, or 57 per cent, were in persons more than 50 years of age. Among the 93 under 50 years of age who died, the two conditions which were a special hazard were pregnancy and rheumatic heart disease. There were 15 deaths in pregnant women, 15 deaths in persons with rheumatic cardiac disease, and 7 deaths in women with both conditions. This means that 40 per cent of the deaths in persons under 50 years of age were in pregnant women and in persons with rheumatic cardiac disease. There were 47 deaths of women between the ages of 15 and 49 years. Almost half the women of childbearing age who died were pregnant.

Following the decline of the epidemic wave of influenza in November, there was a lull during December. In January, 1958, the total mortality rate began to rise again and continued during February. There was little evidence of concomitant illness in the population and one cannot speak of a second wave of influenza. This rise in mortality was not peculiar to New York City. It occurred in most areas of the country. The mortality was almost exclusively in old people and did not affect pregnant women, as can be seen in Fig. 1. While no ready explanation is available for the increase in deaths it seems reasonable to believe that during the epidemic in October the young population was chiefly affected. In the succeeding months the older population was infected. Those who were robust showed little sign of illness, possibly because they were immune to older strains of influenza A. The chronically ill, however, could not resist the assault of the new strain of influenza virus and succumbed. Some validity is given to this hypothesis by the finding by Widelock[5] that 35 per cent of routine blood specimens submitted for Wassermann tests were serologically positive for antibodies to the Asian

strain of influenza virus in November, 1957, and about 75 per cent were positive in March, 1958. These blood specimens were mainly from persons 20 to 50 years of age. They suggest a rising infection rate in the adult population from September, 1957, to March, 1958.

Conclusions

1. In the epidemic of Asian influenza in New York City during October and November, 1957, there occurred 216 deaths from influenza. Ten per cent of these were in pregnant women. If deaths of persons under 50 years of age are considered, almost one fourth of them were of pregnant women. Nearly one half of all women of the childbearing age who died of influenza were pregnant.

2. The only other condition that accounted for a considerable number of deaths from influenza in young persons was rheumatic cardiac disease. There were 22 such instances. Of the pregnant women 7 had rheumatic cardiac disease.

3. Following the epidemic in October and November of 1957 and the lull in December, there was an increase in total mortality without a corresponding increase in respiratory illness. Deaths were chiefly in the old. There was no increase in the mortality of pregnant women during this period.

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MEGALOBLASTIC ANEMIA OF PREGNANCY IN VENEZUELA

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MEGALOBLASTIC anemia of pregnancy is a rare hemopoietic disturbance according to the literature. Nevertheless, it has been found more frequently in India[1-5] and Great Britain[6-16] than in other parts of the world, including Holland,[17] France,[18] Switzerland,[19] Germany,[20] the United States and Canada.[21-28]

Studies of anemia during pregnancy and the puerperium have been carried out since 1953 at the Maternidad Concepcion Palacios, Servicio No. 3, Caracas. Although ferropenic anemia has been observed most frequently, megaloblastic anemia has been seen quite often. This communication will describe the clinical and laboratory data observed in 20 cases of megaloblastic anemia of pregnancy found during the last 5 years.

Material

From 1953 to 1956 there were 16 cases of megaloblastic anemia of pregnancy out of 400 cases of anemia on the Service No. 3, Maternidad Concepcion Palacios in Caracas. The diagnosis of megaloblastic anemia was made in every case from the sternal marrow. A peripheral blood examination, including red-cell count, hemoglobin, packed red-cell volume, platelet count, and white-cell count, was performed before and during treatment.

In 1957 we had the opportunity of seeing 4 new cases and performed other laboratory tests such as reticulocyte count by the brilliant cresyl blue method,[29] serum bilirubin by Malloy and Evelyn's[30] method, serum iron using the bathophenanthroline technique described by Peters and associates,[31] serum B_{12} estimated by microbiological assay as described by Rosenthal and Saret[32] (the test organism being *Lactobacillus leichmannii),* and B_{12} Co^{60} urinary excretion by the method of Schilling[33] with 0.48 microcurie of B_{12} Co^{60} given orally. Radioactivity was measured in a well-type scintillation counter (Nuclear Chicago Model DS-5).

The clinical findings and morphology of the peripheral blood and bone marrow in the last 4 cases will be commented upon, together with those of the 16 cases seen previously.

Results

Clinical Findings.—Eleven cases during the last month of pregnancy were seen and 9 cases a few days after delivery. Most patients showed a fairly good adaptation to the very severe anemia from which they were suffering, suggesting that the anemia had progressed very slowly.

Fourteen patients were multiparas and 6 primiparas. The age varied from 17 to 37 years. Premature delivery was observed in 4 cases.

The past history revealed nothing special concerning the anemia except in 2 patients who had had anemia in their last 3 and 2 pregnancies, respectively.

All these patients were on the poorest economic level and their diet consisted mainly of rice, bananas, corn bread, and black beans; all of them admitted eating meat or eggs only once or twice a week and never a green vegetable. It is important to point out, however, that this diet is consumed not only by the patients described here but by almost all pregnant women attending this maternity hospital.

Besides marked pallor, observed in all cases, the principal clinical findings were slight fever, diarrhea, and edema in 50 per cent of the cases; splenomegaly in 4 cases and hepatomegaly in 5 cases (Table I). Jaundice, smooth or sore tongue, and nervous system disturbances were not present in any of the cases. In 2 cases the megaloblastic anemia was accompanied by toxemia.

TABLE I. CLINICAL DATA IN 20 CASES OF MEGALOBLASTIC ANEMIA OF PREGNANCY

SYMPTOMS	NUMBER OF CASES	% POSITIVE
Fever	12	60
Diarrhea	10	50
Edema	10	50
Hepatomegaly	5	25
Splenomegaly	4	20
Glossitis	0	0

Laboratory Data.—All patients exhibited hemoglobin levels from 2.3 to 7 Gm. per cent. Macrocytic as well as hypochromic microcytic red cells were present in the blood films and the predominance of one population over the other varied from case to case. The term "dimorphic" proposed for this type of anemia, in which macrocytic and microcytic hypochromic populations are both present, may be applied to these cases. Megaloblasts were found in 4 instances.

TABLE II. LABORATORY DATA ON THE LAST 4 CASES STUDIED

		BLOOD COUNT										BONE MARROW					
CASES	AGE	R.B.C. (MILLION/C. MM.)	HB. (GM./100 C.C.)	HEMATOCRIT (%)	RETICULOCYTE COUNT (%)	M.C.V.	M.C.H.	M.C.H.C.	LEUKOCYTES (1,000/C. MM.)	SEGMENTED NEUTROPHILES (%)	PLATELET COUNT (1,000/C. MM.)	ERYTHROBLASTIC SERIES	MEGALOBLASTIC SERIES	BILIRUBIN (MG./100 C.C.)	PLASMA IRON (μG/100 C.C.)	B_{12} SERUM μμG/C.C.	B_{12} (CO^{60}) URINARY EXCRETION (% ORAL DOSE)
E. H.	29	1.5	5.5	16	0.3	106	36	34	5.5	54	280	Neg.	+	0.3	90	300	19
S. S.	28	1.0	3.4	10	0.5	100	34	34	9.7	52	140	Neg.	+	0.6	110	375	11
F. B.	25	1.8	5.9	20	0.4	111	32	29	2.5	58	300	Neg.	+	0.7	80	120	15
A. P.	24	1.6	6.1	20	0.2	124	38	30	3.6	49	350	Neg.	+	0.5	115	400	17

In 11 cases the mean corpuscular volume ranged from 85 to 110; and of 9 cases in which the M.C.V. was above 110, only 5 had a value higher than 120. The mean corpuscular hemoglobin concentration was higher than 32 per cent in 8 cases and between 23 and 32 in the other 12.

The leukocyte count showed extreme variations ranging from 1,700 to 10,000. Most of the patients (13) had a count under 5,000 however. Multisegmented neutrophils were seen in all blood films. Thrombocytopenia was not observed.

The sternal bone marrow showed megaloblastic hyperplasia similar to that seen in pernicious anemia. Megaloblastic and normoblastic series were present side by side in 4 cases.

The 4 cases studied more recently (Table II) exhibited reticulocyte counts below 1 per cent. The plasma iron concentration was within normal limits. The 24 hour urinary excretion of vitamin B_{12} labeled with Co^{60} was between 11 and 20 per cent of the doses given orally. The serum B_{12} showed normal values according to results obtained in 30 normal individuals (from 115 to 450 $\mu\mu$g per cubic centimeter). The normal intestinal absorption and serum B_{12} concentration apparently indicate that the metabolism of this vitamin was not disturbed in these patients.

Treatment.—It is very difficult to follow the patients who attend the Maternidad Concepcion Palacios after they have been discharged. When they improve and feel stronger and more vigorous they do not realize the importance of the follow-up. Thus, only 16 patients with megaloblastic anemia of pregnancy who remained at the hospital could be treated; 4 wanted to be discharged at the begining of treatment and it was impossible to control them properly.

Of the 16 patients treated, 13 were given by mouth 15 mg. of folic acid daily with a total dose varying from 160 to 520 mg. Only 10 patients showed improvement of the symptoms and rise of the red-cell count and hemoglobin level. The average increase of hemoglobin was 5.3 Gm. per 100 c.c. of blood in 30 days. Three patients exhibited no hematological response and no other treatment could be given because they wished to leave the hospital.

The 3 remaining patients were treated with vitamin B_{12}. A good remission, with a hemoglobin increase of 6.4 Gm. per cent, was observed in a patient who received intramuscularly a total dose of 500 μg of vitamin; but the treatment failed completely in the other 2 cases. Unfortunately these last 2 did not receive folic acid afterward.

Although iron deficiency may be expected in some of these patients according to the findings in the blood smears and the low M.C.V. and M.C.H.C., no proper evaluation could be obtained since most of the patients received a large oral dose of iron before the diagnosis of megaloblastic anemia was made.

Comment

Studies on the occurrence of megaloblastic anemia of pregnancy have been reported infrequently. Many authors report a few cases, and others, describing large numbers of cases, do not furnish appropriate data about its incidence. Thus, as shown in Table III, this anemia appears to be less frequent in Holland than in Edinburgh and Dumfries, Scotland. It is seen in Dumfries 15 times as frequently as in Edinburgh. The ratio between the number of cases of megaloblastic anemia and the number of cases of anemia in pregnant women is practically the same in Dublin and in Caracas, and both cities have an incidence of this anemia at least three times as high as in New Orleans.

According to the incidence of megaloblastic anemia of pregnancy reported here (4 out of 100 anemic patients) it seems that this hemopoietic disorder is quite frequent in Venezuela. This incidence cannot be given as representative of the whole population of Caracas or Venezuela, however, since most of the pregnant women attending the Maternidad Concepcion Palacios belong on the poorest economic level. It is important to emphazise that this type of anemia is

rarely or never seen in private hospitals, according to many obstetricians. This differing incidence in public and private hospitals in Caracas apparently indicates that the occurrence of megaloblastic anemia is conditioned by some factor associated with the socioeconomic level rather than with geographic or climatic factors. This reasoning might explain the difference of incidence reported in cities situated in the same country and separated from each other by a short distance.

TABLE III. INCIDENCE OF MEGALOBLASTIC ANEMIA OF PREGNANCY IN VARIOUS COUNTRIES

AUTHOR	PLACE	COMPARATIVE FREQUENCY
Davidson[8]	Edinburgh	42 cases from 1940 to 1951
Israels and Da Gunha[9]	Manchester	5 cases in 6 months
Thompson and Ungley[12]	Newcastle	46 cases in 17 years
Clark[13]	Edinburgh	15 cases out of 31,755 admissions
Lillie et al.[14]	Dublin	14 cases out of 400 cases of anemia (3.5%)
Lindeboom[17]	Holland	2 cases out of 7,561 deliveries
Lund[25]	New Orleans	1 case out of every 100 cases of ferropenic anemia
Bowan[34]	Cresswell Dumfries	9 cases out of 1,850 admissions
Agüero and Layrisse (present work)	Caracas, Venezuela	16 cases out of 400 cases of anemias (4%)

Megaloblastic anemia of pregnancy and the so-called "tropical macrocytic anemia" have some peculiarities in common. Both are considered as anemias due to folic acid deficiency, since this vitamin induces remission in most cases.[35] Tropical macrocytic anemia is mainly seen among pregnant women, but can also be seen, although in lesser frequency, in nonpregnant women and in men. Both conditions can be observed among poor people who have inadequate diets high in carbohydrates and low in protein and in fat. However, megaloblastic anemia of pregnancy has also been seen in well-to-do women whose diet was satisfactory. The increase in nutritional requirements during pregnancy in already nutritionally deficient women has been cited as the important cause in the development of these deficiency anemias. Some other factors such as gastrointestinal upset, repeated pregnancies, hemorrhages, infections, and toxemia may contribute to the increasing demands on hemopoietic factors, or interfere with their metabolism. The clinical findings in both types of anemia are practically the same and no signs of degeneration of the spinal cord are found.

The clinical picture, laboratory data, and response to therapy in the cases presented here made it possible to classify most of them as megaloblastic anemia due to folic acid deficiency. They may also be called either megaloblastic anemia of pregnancy or tropical macrocytic anemia since they were found in a tropical country. The inadequate diet is apparently the main etiological factor in the development of this anemia in our cases; the almost annually repeated pregnancies and the toxemia in 2 cases may have increased the nutritional deficiency, however.

The occurrence of megaloblastic anemia of pregnancy at the Maternidad contrasts with the frequency of other types of megaloblastic anemias observed in Venezuela. Thus, Addisonian anemia is very rare among natives[36, 37]; the sprue syndrome is not seen as often as in other tropical countries like Puerto Rico; and megaloblastic anemia due to deficient food intake is infrequent in public hospitals in Caracas. Of 1,253 cases of anemia from private and public hospitals, collected by one of the authors (M. L.: unpublished observation), only 4 cases of pernicious anemia were found; one of these patients was a native and the other 3 came from northern Europe. Among these 1,253 patients there

were also 3 with the sprue syndrome and 3 with anemia due to deficient food intake who recovered very fast with the usual hospital diet as the only treatment. These data suggest (until further studies of megaloblastic anemia can be made in Venezuela) that the diet of the people on the poorest economic level of this country is not inadequate enough to permit the development of megaloblastic anemia by itself, but at the same time it is not sufficient to prevent the anemia when a temporary increase in demand or disturbance of the metabolism of the hematopoietic factors appears, as usually happens in pregnant women.

In the last 4 cases studied (Table II) the serum B_{12} concentration was within normal limits. Similar findings have been previously reported by Badenoch[11] in 9 cases, by Girdwood[39] in 10 cases, and by Mollin and Ross[38] in 28 of 31 cases. No one has been able so far to explain convincingly, however, why most of these folic-acid-deficient patients show an apparently undisturbed B_{12} metabolism.

Summary

Twenty cases of megaloblastic anemia of pregnancy were seen at the Service No. 3, Maternidad Concepcion Palacios, Caracas. Marked pallor, fever, diarrhea, and edema were the symptoms frequently observed. The blood smear showed macrocytosis as well as microcytosis and hypochromia. The M.C.V. ranged from 85 to 110 in 11 cases and above 110 in 9 cases. The M.C.H.C. was higher than 32 per cent in only 8 cases.

In 3 out of 4 cases the serum B_{12} concentration was normal and the 24 hour urinary excretion of B_{12} marked with Co^{60} after an oral dose of 0.48 microcurie of $B_{12}Co^{60}$ showed values from 11 to 19 per cent.

The literature on the incidence of megaloblastic anemia is reviewed. The incidence presented in this communication (4 out of 100 cases of anemia) is the highest so far reported.

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POLYOSTOTIC FIBROUS DYSPLASIA AND PREGNANCY

A Case Report

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ALBRIGHT and Reifenstein[1, 2] used the term "polyostotic fibrous dysplasia" to represent a syndrome characterized by any or all of the following abnormalities: (1) bone lesions which have a tendency to be unilateral in distribution, (2) nonelevated areas of brown pigmentation of the skin (café-au-lait patches) involving the same side as the bone lesions, and (3) endocrine abnormalities affecting development, growth, and puberty.

The rarity of this lesion as a complication of pregnancy prompted the reporting of the following case. Only one other such case has been found in the literature.

The patient was a 25-year-old Negro woman, gravida i, para 0, who was first seen in the Prenatal Clinic on March 5, 1955. Her last menstrual period occurred on Aug. 25, 1954, and her expected date of confinement was estimated to be June 1, 1955. The prenatal course was uneventful. She was admitted on June 18, 1955, in active labor.

Past History.—There was no history of precocious puberty or abnormality of growth pattern. The patient's menstrual cycle began at the age of 12 and had always been regular. She had sustained two fractures involving the right femur, one when she was 5 and the other when she was 7 years of age. The first fracture occurred when she fell from a swing and landed on her leg; the second, when she fell from a curb and hit her right leg. There had been no other known fractures since that time. The patient had noted the presence of pigmentation which involved the lateral and posterior aspects of the right thigh and coursed over the buttocks and small of the back. These had been present all of her life.

Physical Examination.—The patient was a well-nourished Negro woman in active labor. Examination of the cardiovascular and respiratory systems was negative. The blood pressure was 120/80 and pulse 80. Examination of the abdomen disclosed a full-term intrauterine gestation. The presenting part was vertex and fixed, left occipitotransverse. The fetal heart rate was 150 per minute in the right lower quadrant. Rectal examination showed the cervix to be 90 per cent effaced and dilated 2 cm., with the presenting part at a minus one station. The previously mentioned pigmentation was noted and seemed to be characteristic of the described café-au-lait spots seen in cases of polyostotic fibrous dysplasia.

Laboratory Data.—The patient was Rh positive and the serologic test for syphilis was negative. Routine chest x-ray revealed a peculiarity of the ribs and a skeletal survey was recommended. The survey excluded parts distal to the elbows and knees and showed the fourth, seventh, and eighth right ribs involved in an osteolytic process which had

deformed and expanded the bones, thinned the cortex, and obliterated the normal trabeculations (Fig. 1). Involvement was patchy and diffuse. The entire right half of the bony ilium, the right half of the os innominatum, and the right femur were involved in a similar process (Fig. 2). The seventh and eighth ribs showed evidence of previous old fractures through their lateral arcs. The proximal portion of the ninth right rib was also involved in a similar process. These lesions and their distribution were characteristic of

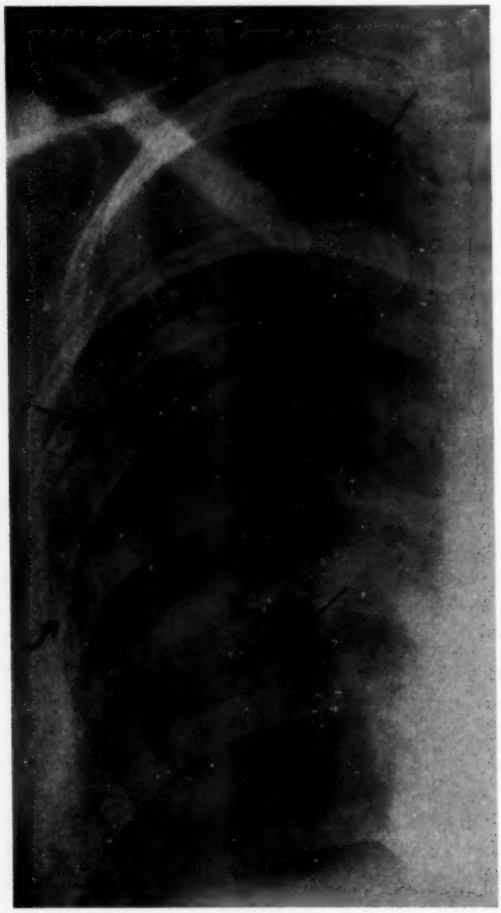

Fig. 1.—Roentgenogram showing an osteolytic process which has deformed and expanded the fourth, seventh, and eighth ribs, thinned the cortex, and obliterated the normal trabeculations.

polyostotic fibrous dysplasia. Routine x-ray pelvimetry showed an adequate gynecoid pelvis with an inlet of 115 per cent and a midpelvis of 120 per cent (Mengert index). A hemogram showed a hematocrit of 40 and a white blood count of 11,800 with a normal differential. Urine specimens obtained by catheterization were negative, as were urine cultures. Blood chemistry determinations indicated that the patient had a normal serum calcium of 5.2 mg. per cent and serum inorganic phosphorus of 2.6 mg. per cent. The alkaline phosphatase, however, was elevated to 10.1 mg. per cent (normal, 1.5 to 4.0 mg. per cent).

Hospital Course.—Active labor started shortly after admission. Because the pelvis was found to be adequate and there was no actual asymmetry resulting from this lesion, it was elected that vaginal delivery be given a trial with immediate postpartum x-ray evaluation of the pelvis to determine whether there had been any damage. After short

first and second stages of labor she was delivered of a full-term male infant on June 18, 1955. Pudendal block and Trilene anesthesia was used and the birth was without incident. Repeat anterior-posterior, lateral, and oblique x-rays of the pelvis were taken immediately after delivery. These showed no point of fracture. The patient had a completely benign postpartum course and was discharged from the hospital in 4 days to be followed in the outpatient department. Examination of the infant revealed no abnormalities.

Fig. 2.—Roentgenogram showing involvement of the entire right half of the bony ileum, the os innominatum, and the right femur.

Comment

The etiology of this syndrome is not known. Albright suggested an embryonic lesion in a sclerotome, resulting in both epidermal and bone pathology. Moehlig and Schreiber[5] had a theory of unbalanced chromosomal aberration. Furst and Shapiro[6] believed in a hypothalamic etiology with a secondary effect upon the anterior lobe of the pituitary. The main theory, however, seems to be that it is of congenital origin, since it usually presents itself in childhood.[7]

Symptoms, as in our case, may be totally absent. Occasionally a history of repeated fractures, pigmentation (usually involving the buttocks, sacrum, and spine), or precocious puberty may lead to the correct diagnosis.

The dominant pathologic manifestations are those of bone absorption, fibrosis of marrow spaces, and substitution of poorly formed and disorderly cancellous trabeculae for the original cancellous and cortical bone. It is because of this resorptive process that pathologic fractures occur. Radiologically, this process leads to multiple spotty areas of rarefaction which resemble cysts with a ground glass appearance and with little demarcation between cortex and medulla.

Laboratory studies, as in this case, show a normal blood calcium and phosphorus with an elevated serum phosphatase. The increase in serum phosphatase activity is chiefly a reflection of osteoblastic activity.

Polyostotic fibrous dysplasia is a chronic disease with little tendency toward progression.

Summary

A second case of polyostotic fibrous dysplasia in pregnancy has been reported. Two of the classic abnormalities were present, namely, unilateral cystic changes within the skeleton, and associated unilateral pigmentation in the skin.

Delivery was accomplished vaginally without damage to the architecture of the pelvis.

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PREGNANCY AND GOUT: A CASE REPORT

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THE rarity with which gout is found among women, and more particularly among young women during their reproductive years, warrants the detailed reporting of cases associated with pregnancy. It is perhaps all the more important in consideration of the dire end results which may occur.

A recent near-fatal case of gout in pregnancy, the only one of its kind known to have occurred at this institution, stimulated a search of the world literature in order to learn the experience of others. This review was all but fruitless, and despite special attention to reports dealing with gout in women,[1, 3, 5, 7-9, 12, 15, 16] only 2 published cases were discovered.[6, 10]

It is generally agreed[2, 14] that gout occurs very infrequently in females, less than 5 per cent of those afflicted being distaff. Since most are past the middle years of life when the disease becomes manifest, it is not unexpected that concurrent pregnancy is quite rare. Talbott[14] writes, "I am not familiar with a single example of hereditary tophaceous gout in a female who has produced offspring after the appearance of tophi." He claims that there is a low fertility rate among married women with gout. That this may be so cannot be ascertained, but one may assume a degree of voluntary sterility in association with advanced years and chronic debilitating disease.

The first of the 2 cases cited was reported in 1953.[6] It involved a 28-year-old gravida with no familial history of gout whose first pregnancy in 1944 was complicated by pre-eclampsia. During the puerperium she developed uremia. Apparently complete recovery followed in the ensuing year, and the patient did well until her next pregnancy in 1947. She again developed all the signs and symptoms of pre-eclampsia and, in addition, experienced progressively severe left flank pain. Delivery was uneventful. The flank pain persisted post partum, and symptoms of gouty arthritis developed. A year later a contracted left kidney was surgically removed, and the diagnosis of gout confirmed. Subsequently, tophi developed and a close correlation of exacerbations of the arthritic symptoms with menses was noted.

The second case, reported in 1956,[10] was that of a 27-year-old woman, also without a family history of gout, whose symptoms began at the age of 19. Radiographical confirmation of the diagnosis was obtained. During pregnancy in 1953, at the age of 24, remission of symptoms occurred. Serum uric acid levels, however, remained slightly elevated. Delivery was uncomplicated.

Markedly increased uricemia was found during the first week post partum, but there was no accompanying exacerbation of symptoms. The latter recurred 11 months later and persisted intermittently thereafter.

Review of the case histories of the 67 female patients with gout (preceding the case herein reported) under care at the Columbia-Presbyterian Medical Center since 1932 failed to reveal any associated pregnancies. All were older women, the large majority postmenopausal, the youngest 38 years of age. That pregnancies were not encountered in a group with this age distribution is not difficult to understand.

C. H. (No. 273971) was a 29-year-old white woman para II, gravida V, who was referred here in the thirty-fourth week of pregnancy because of elevated blood pressure and headache. Pretibial edema had been detected during the previous week.

The patient's first two pregnancies were uneventful; the last two, however, terminated spontaneously in abortion. Her medical history was significant in that she had acute rheumatic fever at the age of 14 without sequelae. During the past 6 years she had a disorder involving both great toes, associated with pain and swelling. Two years previously this had been diagnosed as gout on the basis of blood uric acid levels and x-ray evidence of bony erosions. Both the patient's father and a sister suffered from gout. Her mother and brother were symptom free.

On admission, the blood pressure was found to be 160/100, other vital signs normal. Ophthalmoscopic examination revealed only generalized arteriolar narrowing, without papilledema, hemorrhage, or exudate. The heart was slightly enlarged, but no murmurs could be detected. The lung fields were clear. The size of the uterus was smaller than that expected by dates. The fetus presented as vertex; the fetal heart was audible in the right lower quadrant. Moderate pretibial and sacral edema was noted. All deep tendon reflexes were hyperactive.

Laboratory studies included: hemoglobin 13.9 Gm. per cent; leukocyte count 12,700 per cubic millimeter with normal differential; nonprotein nitrogen 61.6 and 72.8 mg. per cent; blood uric acid 8.3 and 8.6 mg. per cent; serum calcium 9.4 mg. per cent, phosphorous 3.9 mg. per cent, carbon dioxide 19.6 mEq. per liter, chloride 103.9 mEq. per liter, sodium 136.8 mEq. per liter, potassium 4.4 mEq. per liter; serum protein 6.8 per cent, albumin 4.9 per cent and globulin 1.9 per cent; alkaline phosphatase 4.7 units; cephalin flocculation and thymol turbidity negative. The Mazzini test was negative. An LE preparation was negative. Urinalysis showed a specific gravity of 1.017, acid reaction, 1 plus albumin, and a few leukocytes and erythrocytes. The venous pressure was 150 mm. saline. A chest x-ray showed a slight cardiomegaly compatible with pregnancy; abdominal films showed a single fetus in cephalic presentation. The electrocardiogram was within normal limits.

The patient's clinical course on a toxemia regimen of bed rest, salt restriction, and sedation rapidly deteriorated. She developed overt uremia with lethargy, uremic breath, and hyporeflexia. Her blood pressure remained in the 100 to 110 mm. Hg diastolic range. The urinary output fell precipitously.

In view of the ominous portent of events, labor was induced by means of Pitocin infusion 4 days after admission. Following a 6½ hour labor the patient was delivered spontaneously of a 1,550 gram living female infant over an intact perineum. No anesthesia was necessary because of the patient's semicomatose state.

The baby did remarkably well, and as of this writing is approaching her second birthday in excellent health.

Post partum the patient exhibited rapid clinical improvement, despite disheartening laboratory evidence of continuing azotemia, the nonprotein nitrogen levels rising to 98.0 mg. per cent 5 days after delivery. In addition, arthritic symptoms recurred. All signs and symptoms slowly diminished, however, over the next several weeks. Further laboratory investigation yielded phenolsulfonphthalein excretion of 80 per cent, catechol-amine excretion

within normal limits, and basal metabolic rate minus 9 per cent. The patient was discharged 3 weeks post partum, completely asymptomatic and with no detectable residua of her recent illness.

It was felt that this episode had represented an acute uremic condition secondary to gouty nephritis with probable superimposed severe pre-eclampsia. The patient was warned that further pregnancies were inadvisable.

During the ensuing 15 months she continued to enjoy good health. Save for the one mild recrudescence of her gouty arthritis in the metatarsophalangeal joint of the left great toe which occurred post partum, she noted an unusually prolonged period of remission.

Another pregnancy then supervened. During the first 8 weeks of this gestation, she underwent several rather severe exacerbations of arthritis involving both great toes. She presented herself for medical evaluation in the third month of pregnancy.

Except for a moderate tachycardia, physical examination was completely negative. Urinalysis was normal, blood urea nitrogen 12.0 mg. per cent, uric acid 7.7 mg. per cent. Chest x-ray showed no abnormalities.

It was felt that, despite the lack of cardiovascular or renal residua at this time, in view of the fact that the patient had almost died of uremia only a year previously, interruption of the pregnancy was indicated. There was no reason to suspect that the situation would not recur.

The same opinion was expressed by the several consultants who saw the patient, and therefore, in the eleventh week of pregnancy, hysterotomy and bilateral tubal ligation were performed.

Her postoperative course was marred by a severe exacerbation of gouty arthritis, relieved ultimately by intensive colchicine therapy. Otherwise, convalescence was completely uneventful.

Comment

A definitive statement as to the potential interaction of gout and pregnancy cannot be made on the basis of the 3 cases cited. Furthermore, the second case[10] was apparently quite mild and contributed very little to our understanding of this problem.

In so far as the fertility of affected women is concerned, it has been pointed out that very few acquire their disease at a period in life when the reproductive potential is being utilized. Where the disease is manifested early, as in the cases reported, pregnancy seems to occur with normal frequency. These 3 women had a total of 9 pregnancies, resulting in 5 living children, 2 spontaneous abortions, and one therapeutic interruption. Indeed, the last mentioned was conceived as a result of failure of contraception. It appears therefore, that sterility is not directly attributable to gout.

The clinical course of gout may be related to concurrent pregnancy. In 2 of the patients the pre-eclampsia syndrome was notable. Uremia, albeit reversible, followed. Although the symptoms of arthritis largely subsided during the pregnancies in question, post partum exacerbations occurred.

One may speculate on the possible mutually antagonistic effects which two disorders, gout and pre-eclampsia, both associated with uricemia, have upon each other. A recent report[4] suggests that uricemia in toxemia is a result of increased renal tubular reabsorption and occurs in the absence of other renal function disturbances. In gout, on the other hand, most agree[11, 13] that deposits of urate crystals in the renal pyramids produce compression of the collecting tubules with subsequent atrophy of the nephron. In combination, functional

renal insufficiency may result, ending in uremia. The pathophysiological changes of toxemia elevate serum uric acid levels, thereby augmenting the metabolic uric acid disorder characteristic of gout. It seems reasonable, therefore, to expect clinical antagonism between gout and toxemia.

On the basis of observations made here and elsewhere, one may postulate a relationship between exacerbation of the symptoms of gout and estrogen withdrawal. It is known, for example, that symptoms of gout seldom manifest themselves until during or after the menopause.[6] In premenopausal patients, co-menstrual attacks are not at all uncommon.[8] Two of the cases reviewed in this report present further suggestive evidence, in that exacerbations occurred post partum. The theory, however, is not supported by the noteworthy recrudescence of symptoms in the last pregnancy of the third patient.

The relationships here are at best cloudy. It is hoped that wider interest in these problems will result from this presentation.

Summary

The extremely rare association of gout and pregnancy has been examined by the presentation of a case report and summarization of the 2 other cases which have appeared in the literature to date. The possible interrelationship of gout and pre-eclampsia has been discussed, with the tentative conclusion reached that the two conditions are mutually antagonistic. The role of estrogen withdrawal in gouty exacerbations has been implied and, although not clear-cut, a causal relationship is felt to exist.

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DEPARTMENT OF CURRENT OPINION

Pertinent Comments

THE RESIDENCY REVIEW COMMITTEE IN OBSTETRICS AND GYNECOLOGY

THE announcement of the formation of the Tripartite Committee for Residency Review in Obstetrics and Gynecology should be welcomed by all thoughtful members of this speciality interested in postgraduate training. The three immediate participating agencies are the American Board of Obstetrics and Gynecology, the American Medical Association, and the American College of Surgeons. The American Board will represent its three sponsoring organizations (the American College of Obstetricians and Gynecologists, the American Gynecological Society, and The American Association of Obstetricians and Gynecologists); the Council on Medical Education and Hospitals will represent the A.M.A. and the American Hospital Association. The final Committee, therefore, represents directly or indirectly the major organizations in this country interested in the welfare of obstetrics and gynecology. As currently constituted, the Chairman and Vice-Chairman are selected from representatives of the American Board of Obstetrics and Gynecology and the American College of Surgeons, with the proviso that both officers will not come from the same organization; the Executive Secretary will be an ex officio representative of the Council on Medical Education and Hospitals of the A.M.A.

The initial responsibility of the Tripartite Committee will be to formulate the requirements for residency training in this speciality. These requirements will have to be resubmitted to the three parent bodies for approval, after which they will become binding on all participants and will be the recognized residency stipulations for satisfactory advanced training in this field. Thereafter, the committee will be the responsible group to evaluate individual residency training programs on the basis of those requirements and to give approval where indicated.

Actually this move in our speciality is somewhat overdue. General Surgery established such a committee for cooperative review of residency programs in 1953, and committees in Orthopedic Surgery, Otolaryngology, Pediatrics, Plastic Surgery, Proctology, and Radiology have been formed subsequently. Internal Medicine founded such a committee in 1949. The efforts of each of these Review Committees have been singularly successful (J.A.M.A. 165:60, 1957). The areas of Pathology and Thoracic Surgery, together with Obstetrics and Gynecology, have been rather conspicuously absent from the list of those organizing to present a united front with respect to standards of residency training.

The need for a centralized authority in Obstetrics and Gynecology is most clearly illustrated by the fact that during the past year it was possible to find three booklets describing the elements of an appropriate residency, and there were available to the interested candidate two published lists of "approved" residency programs. It is the hope of all that the confusing elements of such a picture will be corrected by the efforts of this joint committee.

Fundamentally each of the three participating organizations has pledged its best effort (and the support of the groups it in turn represents) to achieve such standardization of requirements and to abide by the decision of this new committee. The American Board can now return to its primary function of examining candidates, while the inspection teams of the Council on Education and Hospitals can have the benefit of intimate consultation with representatives of the speciality. While for the coming year it is anticipated that each of the participating organizations will probably continue its own listings and efforts, one would sincerely hope that the new committee will soon take over, on a unified basis, the function of setting the standards for, and of accrediting, the Residency Training Programs in Obstetrics and Gynecology.

TOXEMIA AND PLACENTA PREVIA

An Inquiry Into the Alleged Negative Interrelationship

BIENIARZ, writing in the GRAY JOURNAL early this year (Vol. 75, page 444), has reported a negative association between the toxemia of late pregnancy and placenta previa. He alleges that the coexistence of the two conditions is unlikely, since they appear to exclude one another.

The rarity of occurrence is taken as prima facie evidence for this assumption. The obstetrical literature presents opinions which vary from indifference with regard to this point to statements purporting a possible positive association between these conditions. These are ably summarized by Dr. Bieniarz, and need not be repeated here. Suffice it to say that no other report gives support to the contention in question.

The purpose of the present comment is to test the validity of the theorem by examining the case material at the Sloane Hospital for Women and by re-evaluating the material described by Bieniarz.

During the 15 year period of 1943 to 1957, inclusive, a total of 32,090 deliveries occurred on the Ward Service of the Sloane Hospital for Women. Among these were 176 cases, or 0.55 per cent, of documented placenta previa, and 2,175 diagnosed cases or 6.8 per cent, of some form of toxemia of late pregnancy. The latter includes pre-eclampsia of mild, moderate, and severe degrees, as well as toxemia superimposed on hypertensive cardiovascular and renal disease, and eclampsia.

Among the 176 cases of placenta previa there were 14 with documented toxemia. These included no case of eclampsia, 4 cases of severe pre-eclampsia, 4 of mild and moderately severe pre-eclampsia, and 6 of pre-eclampsia superimposed on pre-existing hypertensive disease. The criteria for these classifications have been previously reported (Taylor, Tillman, and Blanchard: Obst. & Gynec. 3: 225, 1954.)

Since critical breakdown among these various subcategories of toxemia was not available for the years preceding 1951, ward data were more clearly detailed for the 6 year period of 1951 to 1956, inclusive. During this period 16,171 deliveries took place with 98 cases of placenta previa (0.61 per cent) and 848 cases of toxemia (5.2 per cent). The latter included 12 cases of eclampsia and 81 of severe pre-eclampsia, a total of 93 cases, or 0.58 per cent.

Among the 98 patients with placenta previa during this period, 4 exhibited signs and symptoms of toxemia. Of these only one case was classifiable as severe pre-eclampsia. No case of eclampsia occurred.

By comparison, the Gdańsk data reported by Bieniarz on 25,000 births involved 95 cases of placenta previa (0.38 per cent) and 125 cases of severe toxemia (0.50 per cent). The latter included 68 cases of eclampsia and 57 of severe pre-eclampsia. No case of severe toxemia was found among the patients with placenta previa in this series.

The incidence of 0.50 per cent severe toxemia among parturients compares favorably with the 0.58 per cent incidence in our series. These percentages may with certainty be said to represent the expected incidence of severe toxemia in any group of comparable gravidas, including, one must assume, those with placenta previa.

Among Bieniarz' 95 cases of placenta previa, one should expect only 0.48 case; none was found. Among our 98 cases, only 0.57 case should be anticipated; one was encountered. In the larger series, including all forms of pre-eclampsia and eclampsia, a 6.8 per cent incidence of toxemia was determined in the 32,090 gravidas. Among the 176 patients with placenta previa 12 cases (6.8 per cent) of toxemia should occur; 14 were found. It is clear, and is easily verified by chi-square analysis (Table I), that these data offer no significant deviations from expected incidences. This holds for both series of reported data as well as for those from Gdańsk.

TABLE I. TOXEMIA AND PLACENTA PREVIA DATA

	GDAŃSK DATA 1946 - 1955	SLOANE DATA 1943-1957	SLOANE DATA 1951-1956
Total deliveries	25,000	32,090	16,171
Total cases of toxemia	—	2,175 (6.8%)	848 (5.2%)
Eclampsia	68	—	12
Severe pre-eclampsia	57	—	81
Total cases of severe toxemia	125 (0.50%)	—	93 (0.58%)
Total cases of placenta previa	95 (0.38%)	176 (0.55%)	98 (0.61%)
All types of toxemia with placenta previa	—	14	4
Severe toxemia with placenta previa	0	—	1
Expected incidence	0.48	11.8	0.57
Chi square*	0.48	0.44	0.33
Probability of chance occurrence	49%	51%	57%

*$\chi^2 = \Sigma[(f-f')^2/f']$ where f and f' are the observed and expected frequencies, respectively.

It is not our purpose to find fault with the theories expounded by Bieniarz, many of which are provocative and quite interesting. We have merely tested his hypothesis utilizing our own data and have found no support for the contention that placenta previa and toxemia are mutually exclusive disorders of late pregnancy. Indeed, his data, re-evaluated, do not seem to uphold it either.

By using the chi-square test of independence it has been demonstrated that toxemia and placenta previa appear to be neither positively nor negatively interrelated, but are apparently independent and unrelated conditions.

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Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D.

REVIEWS OF NEW BOOKS

Urologic Injuries in Gynecology. By Henry C. Falk. 265 pages, 97 figures. Philadelphia, 1957, F. A. Davis Company. $7.50.

Details of operative technique for the repair of vesicovaginal fistula, stress incontinence, and ureteral injuries sustained during gynecologic surgery are presented and reflect the extensive experience of a well-known gynecologic surgeon. Unfortunately, although the techniques themselves represent a high level of surgical practice, the physical preparation of the book itself leaves much to be desired. The illustrations are clear but inartistically executed and poorly reproduced. The bibliographic references which are scattered throughout the volume have been carelessly prepared, with many inconsistencies in abbreviation forms and spelling.

The most valuable section of the book is that on surgical treatment of vesicovaginal fistula, in which the author has a wide experience. His style is exteremely compressed, and his discussion of the basic principles involved in the various operative procedures is often difficult to follow.

Bibliography on Medical Electronics. Prepared by Medical Electronics Center of The Rockefeller Institute. 91 pages. New York, June, 1958. Published by Professional Group on Medical Electronics. $2.50.

A most valuable addition for the researcher who desires to apply modern electronic techniques. This bibliography contains 2200 references, almost all published since 1950. They are arranged arbitrarily by number with related topics grouped together. There are, in addition, subject and author indices.

While not by any means complete, this volume supplies documentation in a poorly defined interdisciplinary field.

Hermaphroditism, Genital Anomalies and Related Endocrine Disorders. By Howard W. Jones, Jr., and William Wallace Scott. 456 pages, 466 figures, 12 tables. Baltimore, 1958, Williams & Wilkins Company. $16.00.

This text on hermaphroditism and related conditions is an important new book. While the authors state that the book has not been written for any particular group of physicians, it is of particular value to the gynecologist, for it brings together the many aspects of masculinization of the female, including advances recently made in

cytology, hormonology, and the surgical correction of malformations of the female genital tract. It is from the same clinic and follows the classic text, "Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases" written by the renowned Dr. Hugh H. Young in 1937. Some of the illustrations are duplicated from Dr. Young's text. The book represents the combined efforts of Drs. Howard W. Jones, Jr., and William W. Scott, eminent gynecologist and urologist, respectively.

After historical presentation of hermaphroditism, the first portion of the book is devoted to the morphology, physiology, and abnormalities of embryonic sexual differentiation. This section is written by Alfred Jost, D.Sc. The remainder of the book successfully brings together the clinical aspects of true hermaphroditism, gonadal agenesis, congenital adrenal hyperplasia, adrenal tumors and masculinizing tumors of the pituitary gland and ovary. The psychological disturbances which result from these abnormalities are rarely presented or discussed.

Case reports which include illustrations of the general physical appearance, external genitals, operative findings, surgical procedure, and gross and microscopic pathology are used profusely and do much to make the subject matter clear. Many of the illustrations are those of W. P. Didusch, a master in the field of medical art. The case reports on congenital adrenal hyperplasia are particularly well diversified and illustrate broad principles and special points in diagnosis and treatment. Descriptions of many surgical procedures are included. The construction of feminine external genitals and the construction of the artificial vagina are especially valuable to the occasional operator.

While the major portion of the book is of great interest to the gynecologist, the sections on Klinefelter's syndrome, operative construction of masculine external genitals, cryptorchidism, and hypospadias should be better appreciated by the urologist.

There is little in the text on the prostate in the human female, although the case report of a patient with congenital adrenal hyperplasia (Case R. A.) is illustrated by photographs of the gross and microscopic specimen showing prostatic tissue.

This comprehensive book is clearly written and is without question one of the most important additions to the literature on this subject.

BOOKS RECEIVED FOR REVIEW

Fator vascular do endométrio na etiopatogenia das hemorragias disfuncionais. By Carlos Alberto Salvatore. 237 pages, 35 figures, 2 plates, and 2 tables. São Paulo, 1955, Faculdade de Medicina da University de São Paulo.

Obstetrics and Gynecology. By J. R. Willson, C. T. Beecham, I. Forman, and E. R. Carrington. 605 pages, 267 illustrations. St. Louis, 1958, The C. V. Mosby Company. $10.75.

Physical and Behavioral Growth. 26th Report, Ross Pediatric Research Conference. 101 pages, 5 tables, 15 figures. Columbus, Ohio, 1958, Ross Laboratories.

Il Problema clinico della tubercolosi genitale femminile. By G. Dellepiane, C. Durando, and E. Revelli. 163 pages, 23 tables, 10 graphs. Torino, 1957, Estratto dalla Rivista-Archivo di Chirurgia Ortopedica e Medicina.

SELECTED ABSTRACTS

Acta obstetrica et gynecologica scandinavica

Vol. 36 (Supp. 5), 1957.

Johansson, Carl-Johan: Clinical Studies on Sterile Couples With Special Reference to the Diagnosis, Etiology and Prognosis of Infertility, pp. 1-168.

The husbands and wives of 658 sterile marriages from the author's private practice from 1946 to 1953 were studied with the principle that in fertility investigations the couple should be regarded as one biologic unit.

The average age at marriage was 28.9 years for the husbands and 25.8 years for the wives. Only 32.2 per cent of the husbands had sperm counts of 60 million per cubic centimeter and over. The sexual functions studied showed no relationship to sperm density. The inverse relationships between poor motility, as well as poor morphology, and sperm density were statistically significant. The husband alone was responsible for the sterility of the couple in 15.5 per cent, the wife alone in 17.6 per cent, and both spouses coresponsible in 66.3 per cent. Of all the relevant diseases in the history of 658 husbands, orchitis parotidea and gonorrheal epididymitis had the highest incidences, 12.9 and 10.8 per cent, respectively. Grave bilateral abnormalities of the testis-epididymis were found in 72.4 per cent of the sterile husbands, in 56 per cent of the subfertile husbands, and in none of the fertile husbands. In only 6.8 per cent of 370 wives were no fertility-impairing factors noted. Uterine factors were found in 59.7 per cent, with the diagnosis hyoplasia uteri in 37 per cent. Ovarian factors were noted in 48.1 per cent, tubal factors in 31.6 per cent, and menstrual disturbances in 47.8 per cent of the women studied.

Medical treatment of infertility was given to 63 per cent of all 658 husbands in the forms of roborants, Pregnyl, Gestyl, and testosterone propionate. A total of 917 courses of treatment was given, which equals an average of 2.2 courses per treated husband. Organic conditions in the female were dealt with according to standard gynecologic practice.

The conception rate for all 658 studied couples was 18.5 per cent. The first conceptions resulted in 103 infants of whom 92 were born through normal delivery and 11 through obstetric operations. No conceptions were achieved by husbands with ejaculate volumes under 1 c.c. Of abnormal sperm forms, only tail abnormalities had an inverse correlation with conception rate. When occurring simultaneously, a disturbed morphology, motility, and sperm density had the highest fertility-impairing effect (conception rate of 15 per cent). The numbers of simultaneous fertility-impairing factors in the female showed an inverse correlation with conception rate. In the marriages where the husband alone was responsible for the sterility, the conception rate was 24 per cent, and in marriages where the wife alone was responsible, 35 per cent. When couples with one fertile and one subfertile spouse were viewed together, their joint conception rate was 41 per cent, and the conception rate of couples with two subfertile spouses was 28 per cent.

ROBERT L. NESBITT, JR.

Vol. 37, 1958.

Kaern, Teit: Anomalies of Uterine Action and Their Treatment, pp. 26-49.

The author judges all cases of abnormal uterine action according to 3 decisive factors: (1) time of onset, (2) function, and (3) mechanism, in order to obtain a satisfactory assessment of such an anomaly in a given situation. The selection of therapy is

based on the classification of the anomaly in question. In the functional types the desired effects are (1) arrest of localized contractions, (2) arrest of contractions with a wrong trend, and (3) an impetus to contractions. The main principles of therapy are: (1) the use of a combination of oxytocin and a spasmolytic drug (papaverine), and (2) administration by intravenous drip. The spasmolytic drug is given according to the pattern of uterine action.

The present material consisted of a total of 483 cases. There were 270 primiparas. The fetal position was normal vertex presentation in 92 per cent, atypical head presentation in 4 per cent, pelvic presentation in 4 per cent, and transverse presentation in 1 per cent; 12 per cent were postmature. The indications for treatment were partus provocatus (196 cases), premature rupture of the membranes (67 cases), labor incordinata, latent phase (157 cases), labor incordinata, active phase (49 cases), and inertia in the second stage of labor (14 cases). In the group of patients treated because of partus provocatus an average period of 7 hours elapsed between the initiation of therapy and the onset of labor with contractions perceptible to the patient. There was, however, a rather wide variation. Eight per cent were not delivered after a course of treatment. All of these patients were delivered later by resumed therapy or spontaneously. Treatment was very effective in cases of premature rupture of the membranes and resulted in spontaneous delivery in all 67 cases. Treatment was also extremely effective in patients with abnormal uterine action during the latent phase, resulting in spontaneous delivery in 94.7 per cent of cases. A similar beneficial effect was noted in the treatment of abnormal uterine action during the active phase. The pattern of uterine contractions was characterized by a cervical dominance that required the administration of spasmolytic drugs in 70 per cent of the primiparas and in 33 per cent of the multiparas. The treatment also had an immediate effect one patients with uterine action during the second stage of labor.

No maternal morbidity was justly traced back to the method of treatment. One case of rupture of the uterus occurred due to "poor obstetric judgment." In 5 cases strong uterine contractions were induced by the treatment with immediate correction when the infusion was discontinued. A total of 8 babies, or 1.7 per cent, died. Three had died in utero before the mother's admission to the hospital and 3 died during the first week of life from serious malformations. On the basis of personal observations, 93 per cent of the infants had a satisfactory birth cry at once, 5.4 per cent cried spontaneously within a few minutes, and only 1.6 per cent had asphyxia of the first or second degree. Provided the necessary safety measures are observed, as well as proper selection of cases, there is hardly any danger to the mother, and the perinatal mortality and morbidity rates are extremely low.

ROBERT L. NESBITT, JR.

American Journal of the Medical Sciences

Vol. 235, May, 1958.

Kaiser, I. H., and Goodlin, R. C.: The Effect of Ammonium Chloride Induced Maternal Acidosis on the Human Fetus at Term: II. Electrolytes, p. 549.

Nine pregnant women were given 6 Gm. of ammonium chloride a day for 5 to 23 days prior to delivery and 2 others were given 4.3 Gm. early in labor. At delivery, the mean blood pH was depressed to 7.28 ± 0.04 (7.37 in controls) and the carbon dioxide pressure was 37.2 ± 4 as compared to 34.1 ± 4.8 in the controls. More marked effects were seen in fetal (umbilical cord) blood, where oxygen saturation, bicarbonate, and pH were reduced, and carbon dioxide pressure, potassium, lactate, and phosphate were increased.

The fetus normally appears to be in uncompensated respiratory acidosis and this was aggravated by the experimental procedure. The placenta seems to be limited in its capacity for transferring carbon dioxide from the fetus, but this may depend in part upon the fetal lack of carbonic anhydrase.

Comparative serum electrolyte patterns are given for maternal, umbilical vein, and umbilical arterial blood.

LEON C. CHESLEY

The Lancet

Vol. 2, Nov. 23, 1957.

Stewart, H. C., Hughes, W. H., Thomas, E. G., and Nixon, W. C. W.: Trichomonas Vaginitis: Clinical Trial of a Mixture of an Antiseptic With Local Anesthetics, p. 1028.

An antipruritus cream, Locan (amethocaine gr. 1/6, amylocaine gr. 1/12, solution of benzalkonium chloride B.P.C.m 1/3, lactic acid gr. 1/2, and lactose gr. 4), which has been found to have antiseptic action (Hughes, W. H., Stewart, H. C., J. Pharm. & Pharmacol. 9: 431, 1957).

This cream was fashioned into vaginal pessaries and patients with Trichomonas vaginitis were treated by inserting a pessary twice a day for 6 days. If the infestation was not controlled, the period of therapy was extended for an additional 6 days. This therapy was compared with the use of acetarsol pessaries (2 pessaries at night only for 14 days) and the use of one pessary containing phenylmercuric dinaphthylmethane disulphonate (Pentotrane) for 14 days.

In 68 incidents the infestation was controlled every time as opposed to only 47 of 72 incidents controlled by Penotrane and 54 of 79 incidents controlled by acetarsol. Neither this nor any other treatment of one partner alone can control reinfestation.

No evidence of resistance was found and this antipruritus compound, which relieves the intense itching quickly, contains 3 compounds all of which inhibit the organism in vitro. In addition, there is some evidence that "Locan" is effective in moniliasis and this is being investigated further.

DAVID M. KYDD

Vol. 2, Dec. 14, 1957.

Evans, L. A. J., and Ramsey, N. W.: Absorption Studies on Radioactive Iron-Dextran in Pregnancy, p. 1192.

To 7 patients (3 were admitted for termination of the pregnancy at 11, 12, and 18 weeks, respectively, 2 were admitted because of anencephalus during the thirty-second and thirty-ninth weeks of pregnancy, one was admitted at 12 weeks because of an iron deficiency anemia, and one was tested 2 days after a difficult delivery involving the loss of 30 ounces of blood) Fe^{59}-dextran, produced by using $Fe^{59}Cl_3$ as part of the starting iron solution, was given.

The rate of absorption from the gluteal site was similar whether the compound had been given in one or multiple sites or in either side. Within 3 days, 50 to 60 per cent of the injected activity had left the site of the injection. After 10 days the rate of disappearance had been reduced to about 0.2 per cent per day but traces of activity were detected for 6 months. The data suggest that the material is absorbed by way of the lymphatics as shown by the much slower disappearance rate in the patient with arthritis who was partly immobilized by her disease and consequently had little muscular activity and by the fact that, in one instance at least, the Fe^{59} activity in the plasma did not reach a maximum for 30 hours. The activity of the red blood cells steadily increased during the 7 days it was measured.

Inasmuch as surface measurements of Fe^{59} activity must take into account the relatively large accumulation of Fe^{59} that occurs in the liver and spleen between the tenth and twentieth days after injection as well as the accumulation in the regional lymph nodes, the amount of unabsorbed material remaining at the site of injection after the first several days is probably very small.

Transfer of the isotope to the fetus will be discussed elsewhere.

DAVID M. KYDD

Vol. 1, Feb. 22, 1958.

McLaren, H. C., Taylor, C. W., and Attwood, M. E.: Cytological Diagnosis in Gynecological Practice, p. 398.

The previously reported series (McLaren, H. C., Taylor, C. W., and Attwood, M. E.: J. Obst. & Gynaec. Brit. Emp. 63: 801, 1956) has now been extended to include 4,250

consecutive outpatients during the course of 4 years. Each patient was carefully examined clinically as well as by cytological methods. Of all the patients, 481 (11 per cent) were deemed to have suspicious lesions. After extensive examination in the hospital, 85 (2 per cent) were found to have malignant disease. Of the 53 patients with carcinoma of the cervix, the smear was positive in 50 (94 per cent). One of the remaining smears was labeled "suspicious" and the other 2 were found on review to be errors of cytological interpretation. In 3 other instances, however, positive smears were found when careful clinical examination, including curettage, failed to disclose a carcinoma until after repeated examination under anesthesia or exploratory laparotomy.

In carcinoma of the corpus the smear was negative in 7 of the 32 instances, possibly because there is no constant supply of malignant cells in the vagina as a result of stenosis of the cervical canal or of massive dilution of a few malignant cells with blood.

In one of the 16 instances of carcinoma in situ, the smear was negative.

A false positive smear, defined as a positive cytological report where curettage and a ring biopsy or where the histology of the uterus removed by operation does not reveal either uterine carcinoma or carcinoma in situ, was found in 16 of the 94 instances of positive smears. As experience in intepretation was gained, borderline smears that required repetition became fewer (5 per cent of the smears during the first 2 years and 2.5 per cent of the smears during the second 2 years of the study).

Concerning carcinoma in situ, the incidence diagnosed cytologically was 3.5 per 1,000 (16 patients). Even though this method of diagnosis does not find all instances, one of the chief functions of cytology is to arouse a suspicion of carcinoma in situ in the clinically normal cervix. Nine of these 16 patients were treated by deep ring biopsy and 7 by hysterectomy. Observation of these patients extending over 18 to 36 months indicates that deep ring biopsy may be sufficient.

In clinical practice, a negative smear must be ignored but a positive smear must lead to careful curettage and a ring biopsy.

DAVID M. KYDD

Vol. 1, April 19, 1958.

Earn, Albert A., Freer, J. L., and Cairns, D. R.: One Radiograph to Exclude Placenta Praevia, p. 828.

In the absence of hydramnios a single lateral radiograph taken after 34 weeks' gestation was found to be an accurate method of locating the placenta in the upper uterine segment. Of 107 patients who were investigated because of antepartum hemorrhage, malpresentation, unstable lie, or high fetal head, the placenta was identified correctly as being in the upper segment in 90 instances. Early in the study one instance of a second-degree anterior placenta previa was misinterpreted and the placenta was thought incorrectly to be in the upper uterine segment. Of the 90 patients in whom the placenta was found to be in the upper uterine segment, 54 had antepartum hemorrhage (abruptio placentae, 16; circumvallate placenta, 3; erosion of the cervix including carcinoma of the cervix, 3; varicosities of the cervix, 1; polyp of the cervix, 1; no cause found, 30). The belief is expressed that, when indicated, this single radiograph is justifiable because when the placenta is located in the upper uterine segment the patient's anxieties may be allayed and she may be sent home without fear of violent hemorrhage and she need not be kept in the hospital unnecessarily.

DAVID M. KYDD

Vol. 1, April 26, 1958.

Beaven, D. W.: Staphylococcal Peritonitis in the Newborn, p. 869.

Although there had been few recorded deaths from staphylococcus pneumonia or septicemia prior to 1955, 35 newborn babies were admitted to the Christchurch Hospital, New Zealand, with staphylococcus infections between December, 1955, and July, 1957.

Among these were 5 infants with staphylococcus peritonitis, of whom 2 died and 3 recovered. The periods of convalescence of the latter were prolonged and complicated by subcutaneous or other abscesses. The ages of the infants were 49, 21, 20, 14, and 13 days. Possibly infants younger than 2 weeks are protected by the transmitted maternal antibodies. In each instance the clinical course was quite similar, sufficiently so that the diagnosis was made preoperatively in the last 3 instances. The features in common were (1) history of vomiting unassociated with diarrhea; (2) a tender distended tympanitic abdomen with reduced or absent bowel sounds; (3) pre-existing staphylococcus skin lesions. The last were absent in 2 of the 5 infants and present only in the mother of an additional infant. The organism that was isolated was resistant to penicillin in all 5 cases, resistant to the tetracyclines in 3 of the 5 cases, but always sensitive to other antibiotics.

DAVID M. KYDD

Campbell, Janet R.: Duration of Night Feeding in Infancy, p. 877.

The length of time that an infant on "demand feeding" requires to be fed at night varies with the birth weight. Twenty-nine per cent of babies who weigh more than 8 pounds at birth never demanded a night feeding, 27 per cent of those between 7 and 8 pounds, 17 per cent of those between 6½ and 7 pounds, and only 9 per cent of babies who weigh less than 6½ pounds did not require a night feeding. This difference disappears when all the babies are 2 or more months old.

DAVID M. KYDD

Wells, Ronald: Haemorrhagic Diathesis Due to Increased Capillary Fragility Secondary to Ovarian Deficiency, p. 886.

A woman, aged 38, who had had a normal pregnancy followed by 3 miscarriages, had the right cystic ovary removed. Subsequently she developed abdominal pain and vomiting. A second laparotomy was performed and the remaining left ovary was found to be atrophic. There was some blood in the peritoneal cavity and several bleeding points in a band of adhesions were seen. Shortly she developed areas of ecchymoses and abdominal symptoms recurred. She was noted to have an internal congenital strabismus of the left eye and a weakly positive capillary-resistance test but no abnormalities were found in the number of platelets, bleeding time, clotting time, prothrombin time, prothrombin consumption time, clot retraction, plasma fibrinogen, or serum proteins (by electrophoresis). She continued to have ecchymoses, abdominal colic, and occasional blood in the stools despite the administration of cortisone, calcium chloride, and ascorbic acid. Her difficulty appeared to be due to increased capillary fragility rather than to any defect in blood coagulation. Because of the absence of one ovary and the apparent atrophy of the other she was given 40 mg. stilbestrol daily. By the third day the pain had diminished and by the sixth day the ecchymoses ceased to appear. After 17 days the drug was stopped and within 36 hours all her symptoms recurred. Dienstrol (6 mg. daily) was administered and during the next several months she noted only occasional bruising and minor episodes of colic. While in the hospital, incidentally, she was noted to have episodes of petit mal and these were treated with phenobarbitone.

The resemblance of this woman's difficulty to hereditary familial purpura simplex described previously by Davis (Lancet 2: 1110, 1939, and Lancet 1: 145, 1941) was noted and the suggestion is made that estrogen therapy may be of use in this disease.

DAVID M. KYDD

Vol. 1, May 10, 1958.

Bullough, John: Protracted Fetal and Neonatal Asphyxia, p. 999.

Because of a difficult breech delivery the first of twins was subjected to asphyxia estimated to have begun at least 20 minutes before birth when the cord was observed to have ceased pulsating. At birth the infant was pale and the heart rate was 50 beats a minute. Following laryngoscopy which took a further 10 minutes the infant was treated

by endotracheal and intragastric oxygen. The baby began breathing spontaneously after 40 minutes and eventually recovered completely. The second twin was delivered normally and required no particular resuscitation.

DAVID M. KYDD

Vol. 1, May 24, 1958.

*Stone, Frederick H.: **Early Disorders of the Mother-Child Relationship,** p. 1115.

Vol. 1, May 31, 1958.

Wrigley, A. J.: Postmaturity, p. 1167.

Although no new data are presented, three policies for dealing with postmaturity are discussed: (a) laissez-faire, (b) routine termination of the pregnancy x days after the "exact" day because of the hazards of undue size of the fetus, (c) routine termination of the pregnancy because of the possibility of placental insufficiency. All are found wanting: (a) is dead; complete neglect has no place at all; (b) and (c) are difficult to apply because there is no "exact" day useful as the calculated date may be in setting the time when termination must be undertaken in patients with pre-eclampsia or hypertension. A more rational policy is suggested. If the fetus is large, either in health or through disease (e.g., diabetes mellitus), appropriate action should be taken at the appropriate time rather than at the "exact" time. If, when the "exact" time is reached, the patient is healthy but the fetus is small, the pregnancy might be allowed to continue under close observation. The same might be true if the fetus is of normal size except that the period of observation would probably be shorter. An exception might be the case of the elderly primigravida where earlier termination may be desirable. Such a policy avoids routine and allows consideration of the many factors that should influence a decision as to the most advantageous time for the pregnancy to come to an end.

DAVID M. KYDD

Journal of Clinical Endocrinology and Metabolism

Vol. 18, January, 1958.

Little, B., Vance, V. K., and Rossi, E.: Plasma 17-OHCS Levels in Patients With Abnormal Glucose Tolerance During Pregnancy, p. 49.

Pregnancy is one of the most common conditions, other than diabetes mellitus, in which diminished glucose tolerance may be observed. It has been suggested that the increased levels of 17-hydroxycorticosteroids in pregnancy may account for the decreased tolerance for glucose.

The authors studied 120 women during pregnancy, at delivery, and post partum, including analyses on umbilical cord blood. In 83, there was abnormal tolerance to oral glucose during pregnancy but there was no clinical manifestations of diabetes mellitus, and these women were not known to have been diabetic previously. Forty-one of them were treated with 15 units of NPH insulin daily. No difference in plasma levels of 17-OHCS was found between the control, the patients with abnormal glucose tolerance who were untreated, and those with abnormal glucose tolerance who were treated with insulin. It was concluded that there is no relationship between plasma levels of 17-OHCS and the presence of abnormal glucose tolerance during pregnancy.

J. EDWARD HALL

Journal of Pediatrics

Vol. 52, June, 1958.

Mijer, F., and Olsen, R.: Transplacental Passage of the L. E. Factor, p. 690.

The authors report what they believe to be the fifth reported case of probable placental transmission of the L. E. factor from mother to baby. The mother was known

*This article has not been abstracted.

to have had disseminated lupus erythematosus for at least 2 years prior to the delivery of the infant reported. At 20 hours of age the preparation on the peripheral blood was positive. Repeated daily L. E. preparations were all found to be markedly positive (no rosette formations were noted). Weekly examinations remained positive until the seventh week of life, but appeared to decrease in intensity after the fourth week. The child was followed until 8 months of age and no further positive preparations were found. Previously reported cases have demonstrated a similar duration for positive L. E. preparations. This period of time (7 weeks) corresponds roughly to the half life of gamma globulin and appears to support the conclusion of passive transfer of the L. E. factor. Serum complement level determinations appear to fall within the normal range and suggest no evidence of a hypersensitivity phenomenon immediately after birth.

SCHUYLER G. KOHL

Surgery, Gynecology and Obstetrics

Vol. 106, February, 1958.

Boyd, J. F.: Two Possible Cases of Acquired Hypofibrinogenemia in the Newborn, p. 176.

The author advanced the concept that certain neonatal deaths may be due to acquired hypofibrinogenemia secondary to absorption of thromboplastin from the decidual bed by the fetal circulation. To explore this possibility he reviewed the postmortem material from 47 neonatal deaths: 30 term infants who died within 48 hours after birth and 17 premature infants, none of whom had survived more than 6 days. Pulmonary intravascular fibrin deposits, histologically similar to those seen in maternal hypofibrinogenemia, were found in 6 of the cases (13 per cent). Two of these 6 cases in which the fibrin deposits were numerous and extensive constitute the 2 cases reported in the article; one infant was born at term and the other was one of a set of premature twins.

V. TRICOMI

Western Journal of Surgery, Obstetrics and Gynecology

Vol. 66, May–June, 1958.

Rutherford, Robert N.: For Goodness' Sake, Dr. Grantly Dick-Read! p. 187.

Rarely does the editor of this column call attention to editorial comment in scientific journals. Rutherford's challenge of Read's jump on the C.P. bandwagon is timely and written with a gentle but biting pen. Long overdue is the separation of truth and propaganda in the Read thesis, although Rutherford may not be wholly correct in his evaluation of British midwifery.

For those interested in social phenomena this is a choice item of "Grantly Dickism."

LOUIS M. HELLMAN

Items

Institute on Perinatal Casualties

The Schools of Public Health of the Universities of Michigan and Minnesota announce that an Institute will be held in Minneapolis on Dec. 8 through 12, 1958, on "Perinatal Casualties." The Institute will be held for key multidisciplined personnel employed in State Maternal and Child Health and Crippled Children's Program in the midwest regions (V and VI) of the Children's Bureau. Inquiry should be made to the University of Minnesota School of Public Health, Minneapolis, Minnesota.

Grants-in-Aid

The Ortho and Carl G. Hartman grants-in-aid of the American Society for the Study of Sterility, each of $500.00, are available for 1959. Applications for these two grants-in-aid should be sent to the Secretary of the Awards Committee of the American Society for the Study of Sterility, Dr. Robert B. Wilson, 200 1st Street Southwest, Rochester, Minnesota, by Dec. 31, 1958. No application will be considered by the committee unless it is accompanied by five copies of a brief outline of the research project for which the grant-in-aid of $500.00 is being sought.

Erratum

In the article, "The Unengaged Vertex in a Nullipara at Thirty-Eight Weeks' Gestation," by Drs. Burke, Rubin, and Berenberg, in the July issue of the JOURNAL, on page 135, the sentence beginning on the third line should read, "One patient, however, with an inlet capacity of 79 per cent and a midpelvic capacity of 73 per cent, had a low forceps delivery of a 5 pound, 8½ ounce baby after 9 hours of labor in face presentation."